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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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PUBLIC WORKSHOP - ORTHOPAEDIC SENSING, MEASURING, AND ADVANCED REPORTING TECHNOLOGY (SMART) DEVICES

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FDA White Oak Campus
10903 New Hampshire Avenue
Building 31, Room 1503 (the Great Room)
Silver Spring, MD 20993

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M E E T I N G

(8:11 a.m.)

DR. BAUMANN: Hello, everyone, and welcome to FDA's first Public Workshop on Orthopaedic Sensing, Measuring, and Advanced Reporting Technology Devices, or SMART devices. We are very excited to have you here today. True to form, we're starting about 10 minutes late, so we're right on time for government.

We have a very full agenda today, so we'll just get going right into things. We're going to kick things off with a couple great keynote speeches. We're going to get a quick break after that, kind of reset and get ready for our first session, which is Engineering and Technology Considerations. We have four sessions today. They're broken up by panel presentations followed by panel discussion. We've allotted a lot of time for discussion, and it's kind of the theme for the day is sort of collaborative communication between all of our stakeholders. We want you to ask those questions to engage us. We're trying to get to the kind of root of all of these SMART devices that we're starting to see, and we want you to talk to us, we want to have that great dialogue between all parties.

After Engineering and Technology, we're going to take another break, give you guys some time to get some coffee, come on back, have our Clinical and Patient Perspective session. That's going to be the longest one of the day. A lot of clinicians. We have patients here to give their perspective; it's going to be an excellent time. If you're only going to make one, make it the Clinical and Patient Perspective session.

After that, we get a 45-minute break for lunch, come on back, talk about Cybersecurity in Healthcare, again, panel presentations followed by discussion. Take another break. Then we're going to close out the day with Regulatory Considerations and some closing remarks and just kind of bid you adjourned.

Now, throughout the day, we encourage you, we need you to please leave feedback.

We have a couple of mechanisms to do this. If you go to www.regulations.gov and search for the docket number of this workshop, which is FDA-2018-N-0235, and then click on "Comment Now," leave your comments right there, or you can go to the *Federal Register* notice and just click on "Submit a Formal Comment," they call -- get funneled to the same bucket, but please leave your feedback there if you would like. Do it as you -- as the questions come to you throughout the day or save it all for the end, it makes no difference, but please leave that feedback. Our goal here is to generate a white paper when we're all done, and the comment period closes on May 29th, so please do leave that feedback.

We are going to be archiving all of the content that you see today, so all the presentations, the PowerPoints, the conversation, all the transcripts will be available on the FDA website, so it is there for you to look at again, should you choose.

And, of course, we want you to have internet access today. The public network in the Great Room is FDA-Public and the password is publicaccess, so please take advantage of that.

Now, this has been a long time coming for us. We've had a team of internal FDA organizers kind of working for the past couple of months to bring all of this together, and we're very excited to have everybody here. We had about 250 advance registrants plus the people registering online and showing up the day of. But it just wasn't -- our work was also the collaboration of external stakeholders, particularly the Center for Disruptive Musculoskeletal Innovation. And to talk a little bit more about that and the great work that they're doing, I would like to introduce to you Dr. Jeff Lotz from the University of California, San Francisco.

(Applause.)

DR. LOTZ: Thank you, Andy.

So this meeting has really been, I think, a fun collaboration between the CDMI, which

is the National Science Foundation Industry-University Cooperative Research Center to which Anton Dmitriev is an FDA liaison. And so we have, over the last 4 years, supported a number of projects which are sensor related, one on, for example, detecting fracture healing with the impedance sensor that Michel Maharbiz, who is one of our speakers today, was a mentor. Another was track-wearing sensors to track patient outcomes after surgery, a project that Stefano Bini was a mentor. We've also had student technology scout presentations, one of them on orthopedic, SMART orthopedic devices, which was mentored by Aenor Sawyer, who's one of our speakers today.

And so the CDMI has been, I think, really valuable in stimulating discussions around these technologies, particularly around where is the technology headed, where's the value to patients and clinicians, and what are the potential regulatory and/or safety related issues. And that was really the nidus of this discussion that Anton suggested we collaborate for.

So it is, I think, going to be a really interesting day, and I want to also introduce, I think, Andre Marshall here, who is -- his hand is in the back. He's the program director for the IUCRC program at National Science Foundation. So if you have any interest about that program, please either talk to him, Vijay Goel, who is a co-director with me, or myself.

And so I'd like to introduce Michael Margerrison -- excuse me, Edward Margerrison, who is the Director of Office of Science and Engineering here at FDA, and he's going to talk a little bit about the FDA perspective and the value we're hoping to extract out of this meeting. Thank you.

DR. MARGERRISON: Good morning, everybody. I would like to first of all welcome you on behalf of the FDA, the Division of Orthopedic Devices, Mark Melkerson, and myself, Ed Margerrison. I'm the Director of the Office of Science and Engineering Labs here at the FDA.

I think we've got an enormously exciting day today. We are represented in the room by industry; of course, government; academia; the media; and we have two very, very special guests. We have two patients present with us, and I think that they are absolutely the most important people in the room because if we're not doing it for them, then I don't know who we are doing all of this for.

The workshop objectives I'm not going to read out. I just wanted to highlight that this is very much a day of discussion. We have microphones around the room. It's not a series of lectures; we have lots of panel meetings and hopefully a lot of great discussion going on. That has to be the theme of the day because the intention of the overall day is to come to the same common understanding of where we are in this incredibly exciting field. There is a long, long way to go, but if we start at the same starting point, we believe that we can all accelerate some of the truly innovative ideas that are coming through.

I want to take a few minutes just to introduce CDRH, the Center for Devices and Radiological Health. That's one of the major centers within the FDA, and many of you in the room probably aren't familiar with what we do. We are, as I usually joke, in the cheap seats at the back. You can see on the left of the screen, this is where we're actually currently sitting, up near the Commissioner's office. We're way at the back. We don't deal with drugs; we don't deal with food or any of that. We deal purely and simply with devices, radiological health, and in vitro diagnostics, and we're extremely proud of that.

To put that in perspective, we actually oversee 190,000 medical devices that are currently on the U.S. market. We oversee 18,000 medical device manufacturers who manufacture their devices in over 25,000 facilities worldwide that we are responsible for ensuring they are producing quality and safe products for the U.S. population. We receive a quite phenomenal amount of premarket submissions and postmarket submissions and signals, and we do it all with 1,800 staff. And as Center Director Jeff Shuren and I joke,

that's about a third of what Caesars Palace has, and we quite often say we couldn't even run their kitchens let alone something that's useful.

So our mission statement is very interesting at CDRH. It actually has words like "facilitate" and "innovation" in it, and I think that's very, very different from a few years ago, and it's a really important part because I think, genuinely, that any fences between industry and the FDA are maybe not completely zero but they are massively lowered from where they were a decade or two ago. And we're really excited by that. I genuinely believe that everybody in this room is on the same side, to try and get innovative technology in to U.S. patients. We want to continue promoting that.

It's important to note that it doesn't mean that the safety requirements are any the lower, based on wanting to accelerate and innovate new technology and get new products onto the market. Those barriers, if you like, are still exactly the same; we have to do the right things. At the Agency, we spend our entire life balancing the benefit and the risk of early products, and including those that are already on the market. That's what we all do for a living within the whole Agency.

We don't believe that innovation and safety are contradictory to each other. If we use those together and actually evaluate the benefit-risk in an appropriate way, we can get the best devices onto the U.S. market as quickly as possible. And that's the basis of the medical device safety action plan that was announced by the Commissioner a week or two ago.

So within CDRH, I run an office called OSEL, for short, the Office of Science Engineering Labs, and you'll find many representatives of OSEL in the audience today, including Andy, Anton, and Shiril, and some of our other colleagues who have put this workshop together.

Our job is to say we have no reason to say we don't know. A lot of that is really

future-proofing the Agency for technologies that are coming down the road in the future so that when sponsors and manufacturers come to us with new devices we're not blindsided, we're not saying we don't have to evaluate that, we don't know what questions we even want to ask you. If we were continuing to operate in those sort of terms, we would simply be a blockage on the way to new products, and that is not what we're here for at all. So we spend a lot of time on standards, developing new methods, doing a lot of technology planning and access to try and work out what's going on. So today is a really important part of that whole process for the Agency.

This is an area that has had a fairly slow start. It's a little like 3D printing, from that perspective. It's a technology that has been around in other industries for quite some time and at some stage or other is going to make a break into the mainstream of devices. And one of the things for today is going to be to make sure that we all have a common understanding of that so that we cannot necessarily answer many of the questions, but to at least identify what the right questions are and then we can take it from there.

We actually worry about an enormously ridiculous breadth of technologies within the FDA, within CDRH, and certainly within OSEL. The number of devices is 190,000, as we said already. They all use different technology within them. So today, I think, is a really important place as well, because we will be talking about digital technologies, we'll be talking about orthopedic technologies, but the important point from our perspective is that a lot of that learning can be used in many, many other industries and other product areas as well. We're seeing some of this advance in things like physiological closed-loop monitoring systems. And really the time for orthopedics is right now, and we want to play our part in making sure that we are continuing.

So as I said, SMART implants have been around for a while. When I was in industry a few years ago, we always used to think, well, wouldn't it be great if we could sense

something and get an implant to do something constructive? But to be honest, back in those days we really didn't know what we were trying to sense or what we were trying to do. We knew it would be a great idea to try and prevent nonunion fractures, for example, from occurring. But how do we actually do that? In those days, we didn't know. We're beginning to think now that the time is right for orthopedics to be taking some of those steps, and I think we're going to hear from many, many people today about how those steps are becoming a reality right now, and they are already here.

So as I said, we don't have all of the answers. We may not have many of the answers at all. We want today to be a discussion between academia, between industry, between government agencies, and of course, the patients, and see if we can actually start setting the stage for getting those answers and at least setting the right questions so that as the technologies are being developed into products, we can promote those and make sure they have a relatively easy passage through the regulatory process.

And as Andy said, we do have a *Federal Register* notice. I'm not going to do a quiz and ask you if you all know the docket number. I'm sure there will be plenty of people around who can actually answer that for you.

So on that, I'm going to stop. I would very much like to introduce our next presentation speaker. Dr. Euan Thomson is the global head of R&D for Johnson & Johnson Medical Devices. By training, he's a medical physicist, and amongst many other responsibilities, he has responsibility for orthopedics and also for digital technologies within J & J. In his career, he's had extremely responsible positions in many companies and in funds and VCs in terms of robotics, in terms of big data, and in terms of wearable technology as well. So he's a perfect person, I think, to kick this off from the industry perspective. So would you please welcome Dr. Euan Thomson.

(Applause.)

DR. THOMSON: Well, thank you for that introduction. And I also just wanted to start things off really by thanking the Agency and particularly the organizing team for pulling together such an amazingly diverse audience and bringing to the fore this incredibly important subject. I think this is timely, and I think the open discussions hopefully that we have today will be as valuable as the presentations in bringing out people's feelings and thoughts around this.

So when I mentioned to my wife, who is from Connecticut and a marketing professional, that I was going to be speaking at a SMART devices conference, she advised me that the best way to sound smart myself was to speak in an English accent.

(Laughter.)

DR. THOMSON: So I've been practicing, and I will be delivering the whole thing in an English accent, and you can tell me afterwards how I've done.

But, seriously, when I think about technologies and the impact they can have in orthopedics, it's not about the technologies themselves, and I think as we think about what's possible today in terms of sensors as well as in terms of non-implantable technologies that we're surrounded by all the time, such as wearables, there's a great tendency to focus on those technologies as being the answer. And, of course, they're not, and that can take us in the wrong direction. What we're really trying to do is improve outcomes, and technologies are about outcomes.

When we look at orthopedics, despite the fact it is an evolved space, there are still a lot of things that aren't perfect. There are still, in the field of spine, for example, a very high proportion of patients who don't achieve the outcome that they hope for. Revision rates are higher than we'd like for joint replacement. And we know that there are differences between surgical outcomes according to different -- depending on different sites and different surgeons; the experience of those surgeons can make a difference.

So there are unanswered questions that are out there. But, traditionally, when we try and answer those questions and we try and dig into how we can improve outcomes, we've just focused on the devices themselves. We always come back to how can we improve the device, how can we make the device better, as a way of equalizing and improving on outcomes.

The reality is when I think about it, I think about three major buckets, and some small areas as well, but three major buckets that influence outcomes. The first is the device itself. But the second is the surgical practice, the surgical procedure, the individual surgeon's surgical variations that take place. And the third is, of course, the patient themselves: patient selection, patient preparation, patient rehabilitation. All of those things have an impact on outcomes. So we're really dealing with an area where, of those three particular categories, the implant, the surgical procedure, and the patient, where we've really historically only been focused on one, the device.

And I think now is the time to broaden out, and as we do that, there's also an opportunity, I think, to broaden out our perspective on outcomes. We can think more about mobility today, where we can measure it and quantify it. We can broaden out and think about what really matters to patients when they come in for surgery. Very often they're not really looking for the same types -- well, they're not measuring the outcome in the same way that we as professionals in the industry would measure outcome. They've got very human things that they're trying to measure, but those things have been very hard to quantify in the past, and so we've tended to avoid them.

But our opportunity today is to include them in the mix. We have technologies that have been brought to bear in the operating room which can capture some of those surgical variations, things like robotics, navigation, digital check sheets, post-surgical analysis of imaging, and these are real technologies that exist today. All of those things could be

brought to bear to analyze surgical variation. But we also have things available to us now that can monitor lifestyle, and there are things which we can use to quantify as opposed to use of qualitative metrics around whether the patient has really achieved what they would like to achieve.

So we should talk about sensors and implantable sensors, and I think we should also consider that we can use a whole range of sensors that aren't inside the patient as well, ultimately IoT, to where figuring out whether we've really been able to return somebody to the life that we would like to -- that they would like and they were hoping for.

And if we can do that, our opportunity is huge. We have an opportunity to connect across the continuum of care. So if we put on the same data architecture information about the patient pre- and post-surgery, their activity levels, quantify their lifestyle before and after, and benchmark that -- and we can capture what happens inside the operating room using, in parallel, using the digital technologies which are coming to bear inside the OR, we could look for clusters of patients with good outcomes, clusters of patients with bad outcomes, and we can trace them back and figure out whether it was surgical variation that made the difference or whether it was something to do with the patient or something the patient did that actually made a difference and influenced outcomes. And then we can improve.

And this is a new era. When I think about things generally up until now, I think of this information flow as being kind of one dimensional. We capture information about what patients do, but we never really link it back to what happened in the operating room or the activities that might have influenced the outcome.

And if we're successful in this, we can really make a difference. We've been looking at this quite heavily lately, just the difference between what we might traditionally have considered a good outcome, such as radiographic fusion, and the outcome according to a

patient. Very few patients, if you asked them what they're hoping for from their surgery, would talk about things like radiographic fusion. They would have very human goals: Can I pick up my grandkids? Will I ever run again? Can I comfortably take the stairs? Can I get out of a chair? Those are the things which we should be measuring our successes against, as well as the traditional medical ones. So technologies can enable us to do that; they can broaden our perspective, and we can quantify those outcomes for the first time. And I think that really is a big opportunity.

But as we go down this route, we have to be careful. The same standards that we've applied to the devices themselves need to be applied to every technology that we use to draw those conclusions. So, for example, if we want to quantify mobility but we're doing that using an over-the-counter wearable or a step counter, as I've seen a proliferation of both companies and organizations doing, we can go seriously off track. We could be drawing conclusions about mobility being related to something that happened in the operating room or something the patient did and guiding people in completely the wrong way. So we have to apply the same standards to every step in the process, everything in this data continuum, including the sensors and including wearables and including the data that we gather from the operating room.

And, of course, the other cautionary note is around data security. If we start creating this data infrastructure and create an environment where we can gather new learnings, then we need to be very careful that we're now -- that we do protect the patient and look after their data. And it's not the thing to say, but I think it's something that we really need to take extremely seriously.

So, in conclusion, we really do have the opportunity to change the trajectory of healthcare using technology, SMART sensors, and a range of digital technologies both in the operating room and beyond the operating room, and connecting them across the

continuum of care is what's really going to give us the data we need to analyze and draw the insights that we can use to change that trajectory.

So in doing so, we can also broaden our definition of success, but we need to be cautious. Just because a device today may be widely utilized, such as a wearable, and it's accessible and over the counter, it doesn't mean that's the right thing to embed it inside a medical service.

Data security is paramount and I think, as exemplified by today, collaboration between FDA, industry, healthcare providers, academia will be required to support this journey.

So thank you very much. I'm really looking forward to the day, and I guess now we are headed into a 5-minute break. Thank you.

(Applause.)

DR. DMITRIEV: Ladies and gentleman, we'll reconvene at 8:45, so we'll have about 10 minutes for our break right now.

(Off the record at 8:34 a.m.)

(On the record at 8:47 a.m.)

DR. DMITRIEV: Good morning, everyone, again. My name is Anton Dmitriev. I am a director of one of the divisions in the Office of Science and Engineering Laboratories, and I'm also one of the co-organizers of this workshop. It really gives me great pleasure on behalf of our organizing team to welcome you on this wonderful day in Maryland to discuss the cutting edge of orthopedics.

And to start off the session for engineering/technology overview, I'm honored to co-moderate the session with Professor Vijay Goel, who is a distinguished university professor and also McMaster-Gardner Endowed Professor of Bioengineering at the University of Toledo. Dr. Goel is a pioneer in understanding the spinal disorders from the

academic perspective, but he is not only an academician, he certainly drives the innovation through a number of startup entities that have taken stem at the University of Toledo, looking at sensor-enabled technologies both in orthopedic care, spinal orthopedics, as well as infection prevention.

So, with that, Dr. Goel, let us get going. Our first speaker of the day will be Professor Mark Allen, who comes to us from the University of Pennsylvania. Dr. Allen is a pioneer in the field of micro-electro-mechanical systems, or MEMS technologies, as well as nanofabrication technologies. He will discuss with us the current landscape of orthopedic -- of SMART technologies in orthopedics. And please welcome Professor Allen.

(Applause.)

DR. ALLEN: Well, thank you very much. And I'd like to thank the organizers for inviting me. I've been looking forward to this for some time. I have to admit, though, that when I was first asked to give a talk with this somewhat lofty title, I said, well, I think it's going to be hard for me to be able to give a tree version of the orthopedic landscape, so perhaps it's better if I give a forest sort of version.

So with that disclaimer, what I said that I would try to achieve in this presentation is first to start off with maybe a little bit of history as to why now is the right time for this. I think we heard that earlier in the keynote talks, and I'd like to give you from the technology perspective why now is the right time, and then how some of the miniaturized sensor technologies that people like myself work on might be applicable to SMART orthopedics, and then give you a couple of examples of research-level projects, so things that perhaps are coming down the pike. I can't really tell you all the wonderful things that you are doing in the SMART orthopedic space -- you know more about that than I do -- so I'm purposely not going to try to do that in this presentation.

So first let me define what I mean as MEMS or medical microsystems. The folks in

the MEMS, or micro-electro-mechanical systems field, talk about using micro and nanofabrication techniques. To us, that means techniques that are perhaps first cousins to the techniques used to make integrated circuits, to make mechanical structures, sensors and actuators that can interface with parts of the human body, either in vitro or in vivo, to diagnose or treat disease. And what I'd like to do is to suggest that these medical microsystems are at a technological level that they're ready to be utilized, and also to give you a perspective of why it is that these systems could be very useful.

So, first, maybe a few observations, and, again, I think we heard this previously. People are living longer and longer, and maintaining quality of life as average age increases is in great demand. But in some sense we are running into a little bit of a problem, right? Disease states are becoming more complex. I think that's a consequence of success. I think that as relatively simpler conditions are addressed, the more complex ones now have time to emerge. And so that means our job continues, right? We have to work hard for this, and one way that we can try to continue to improve quality of life for people is to get more information into the hands of physicians.

So let me start off, then, with an example. If this is such a great idea, why hasn't it been done before? And, of course, the answer is it has; people have looked at this for a while. This is a picture of someone's finger here, and I apologize for the bad image, but I will explain why it's somewhat poor quality in just a moment. So here's a person's finger, and on his finger you will see three devices. The smallest one is a couple of millimeters or so in diameter, and what these devices were intended for were to be implanted in the eye for measuring intraocular pressure for patients with glaucoma. And so these devices were fabricated. You can find this in the literature, and if you look far enough back, you'll see that these devices were published in April of 1967. So it's not that this is suddenly a new idea. It's not that people are suddenly thinking about it now. People have been thinking

about it for 60 years, right?

Why hasn't it been widely adopted? Well, let's look a little closer. And I'm not going to search through or I'm not going to go through all of the details of how this device is made, but let me simply point out that part of what's required for these devices are fine windings, and the way these windings were made was somebody took a piece of sticky tape and a long wire and wound it by hand onto this piece of sticky tape and then, in a triumph of engineering, sealed this whole thing together. And it did work. You could show that there was sensitivity of this sensing device as a function of pressure so that you could actually get information out from the interior of the eye.

So why wasn't it adopted? Well, if you look a little closer at what happened, there were three major issues, right? One was stability. So this device wasn't hermetically sealed; they didn't quite know how to do that. Tissue would grow on it, and that would affect the readout that could be achieved. There would be corrosion, fatigue, biocompatibility needs, restricted material set, and then the readout distance required you to be very, very close to the surface of the eye in order to read things out. But, of course, if we're talking about orthopedic applications, we're talking about trying to read out information from relatively deep within the body.

So 1967 there was not a chance for this, but something interesting has happened in, you know, the past 50-60 years. And not only have these individual fields advanced, but they've converged; they've all matured kind of at the same time, which is really interesting.

Three things happened, I think. The first is we now know how to leverage integrated circuit technology to build these small-scale devices with much, much higher repeatability, reasonable precision. We have this enormous infrastructure that's available to us from the silicon-integrated circuit folks that we can leverage to build these small sensors and actuators.

The second thing that has happened is that we've gotten really, really smart about using miniscule amounts of power. I like to tell people that the wireless charging that we're starting to enjoy now for our iPhones and such is a product of the last century, and when I mean the last century, I don't mean the 20th century; I mean the 19th century, right? This is when magnetic resonance for transfer of power wirelessly from one place to another was demonstrated.

The problem is that back then you couldn't do much with the amount of power that could be transmitted. Now we can do enormous amounts with watts or even milliwatts. Milliwatt is a lot, so now we can start to think about harvesting energy from the environment, harvesting energy from the body, to allow these implants to be able to operate for relatively long periods of time. We've also made tremendous advances in batteries. So if we have a relatively limited duration medical need, we have advanced batteries available to us.

And then the third thing, perhaps the most important thing, has been the tremendous growth in the wireless electronics technology. So I didn't show you the circuit diagram for the readout of Collins's eye sensor, but it has vacuum tubes in it and was very advanced for the day. But obviously we now have the technology to be able to ultraminiaturize the kind of circuitry that we need. We have unprecedented sensitivity to signal levels. So even though signals are highly attenuated within the body, it's possible to read them out.

And perhaps most importantly, what do we do once the information is out of the body? Well, we have this global information net where information can be relayed to physicians in almost real time for action to be taken.

So let me focus now the remainder of my presentation on this piece, the MEMS, and some of the things that are coming based on this integrated circuit manufacturing

technology so we can see how we might be able to apply this to SMART orthopedics.

So, first of all, if I -- I've already defined what MEMS are. I've said that they're first cousins, if you will, to integrated circuits. They exist in our lives everywhere.

So, for example, I can make microphones which, at their simplest, are a moving plate and a stationary plate that I can measure the distance between, and as sound waves hit the moving plate and move it back and forth, I measure that distance and it gets turned into an electrical signal.

Pressure sensors that are in everybody's car, for example, to measure pressures in intake manifolds to keep the cars running optimally.

Accelerometers to do either mundane things like tell your iPhone screen whether or not to be horizontal or vertical, but also do things like step measurement and such.

Chemical sensors: This is a picture of the prototype contact lens from Google, the idea being to measure the chemical concentrations of certain things in tears and to be able to then wirelessly transmit that out.

And we also have implants. So these are some endovascularly implantable wireless pressure sensors that can be used for measuring pressure in the pulmonary artery and allowing patients with congestive heart failure to have their medication more optimally titrated and keep them out of the hospital, avoiding decompensation.

And these are approved, these products, so they're available now. It is possible to think about taking these MEMS-based systems and putting them not only on the outside of the body as part of all of these wearables but inside as implants.

So other than being small, is there anything else that these MEMS might be able to do for SMART orthopedics? Well, I tried to think a little bit about what the advantages are, and I don't expect you to read all of this, this is for later perusal, but there's really four different ways that MEMS can be advantageous in general and in SMART therapeutics in

particular.

I think that this one, where devices can be made so small that it gains a performance advantage, obviously, we want something that has size scales that match the anatomy that we're trying to interact with.

And this one, where we can start -- the top one, where we can start to think about large numbers of interconnected devices, multifunctional devices that are still overall relatively small in size. So now we can think about measuring multiple modalities and getting lots of information out.

So let me give you a couple of examples of things that we're working on in our laboratory. So these are just -- these are not things that are anywhere near ready to bring here to put in front of the FDA, but just to give you an idea of some research projects that may at some point come forth.

So the first question that we were looking at is, is it possible to create biosensors that will allow us to detect inflammatory markers? You know, is it possible that we can look at systemic measures of health as a way to see how healing processes are progressing?

So these are some impedance-based sensors that we fabricate, and to give you an idea of size scale here, each one of these little holes is about 5 µ or so in diameter, and the entire sensor itself, the tip is about 100 x 100 µ on the side. And by monitoring the impedance of these individual wells, it's possible to monitor the absorption of antibodies and antigens on the surface of these devices.

We can think about other possibilities as well. This is an oxygen sensor that we've been fabricating. You see sort of a traditional three-terminal device, but the idea here is that this oxygen sensor could fit within a healing bone. We have -- I'll show you in a moment -- a segmented bone defect model that we've been working with, together with Bob Goldberg's lab at Georgia Tech, to monitor the healing of bone. And we have a

hypothesis that if we can monitor the oxygen concentration in that healing milieu, we can get a better understanding of what sort of factors go into perhaps speeding the healing of bone. And so it's possible to microfabricate these, there's not a size scale here, but this is about a couple of millimeters on the size. It's relatively large by our MEMS standards, and we can get linear relationships between oxygen concentration and something that we can measure from this sensor, which is an output current, allows us to be able to look at that oxygen concentration in that milieu.

And then finally the last example, this is that segmented bone defect model I was talking about where we remove a section of bone and replace it with a fixation plate that is studded with sensors that allow us to measure strain and also oxygen, as I showed you before. It's completely wireless. We can get a wireless readout, external to the mouse or rat here, of strain, and we can have this rat sort of walk around, if you will, in an environment and measure the strain on this fixation plate as it is moving. So is it possible to think about ways that we can identify when calluses form, or is it possible to even guide therapy by looking at the changes in strain at the bone relative to external strain?

So, with that, I think I will conclude. I hope this gives you an idea of some of the landscape and why it is that we are gathered today, right? Technologically we are ready, in addition to medically we're ready.

So just a few things that might -- this is my last slide -- a few things that might be coming down the pike that we might want to look for. Often it's true that the healing of bone is a transient condition, right? An acute, relatively acute condition. We might want to think about devices or sensors that monitor that condition that are transient themselves, that do their job and then disappear when they're no longer needed.

And these sort of devices are now coming out of the labs. This is a wireless pressure sensor made out of biodegradable materials, for example, that can sense pressure, and

then when it's no longer needed, it dissolves away much like a suture would do.

Is it possible to think about combining multiple modalities into a single sensor, something that could sense, for example, oxygen and strain in one device or even biochemical modalities in that same device?

And then, lastly, is it possible that we could think about something that isn't just diagnostic, but could we think about devices that could also help guide and institute therapy?

So I think there is a lot available to us. The technology is ready, it has converged, and we are eager to get it into the hands of people who will use it to improve the human condition. Thank you.

(Applause.)

DR. DMITRIEV: Excellent presentation. Thank you, Professor Allen.

Our next speaker is Professor Shuvo Roy, who comes to us from the University of California, San Francisco. Dr. Roy is the director of the bio-design laboratory at UCSF and is also an engineering lead for surgical innovations. Dr. Roy has also started a UCSF pediatric device consortium, which is an FDA-funded program, to facilitate development of pediatric devices. And with that, we're going to try to shift gears and talk about the application of technologies in the three different sensors, basically just going from passive monitoring to diagnostic applications and maybe closed-loop systems.

Dr. Roy.

DR. ROY: Thank you very much, and thanks to Jeff and Vijay and the rest of the FDA team here for inviting me. I'll start off by saying that some of what I'll show you today is actually not the research I do now; some of it has been done in the past. And with that, I should start off with my collaborators who have actually worked with me over the years. So I'll talk about two aspects of my research career, one aspect when I used to work at the

Cleveland Clinic almost over a decade ago, and many of the ideas I'm going to talk about today actually originated in the early 2000s. But for a number of reasons, maybe medical, maybe technical, maybe regulatory, the field was not ready to advance these ideas. And, secondly, I'll talk about some of the ideas we're pursuing under the auspices of the Pediatric Device Consortium that may have some orthopedic-like applications.

So my colleagues are across both places, but the speaker after me, Dr. Ferrara, is actually in the audience, and some of these ideas were attributed to her.

So I would like to categorize these approaches maybe in three different ways. I said monitoring, let's get the data. Let's not worry about trying to make decisions from the data, but in this concept we'll try to get as much data, and in this age of big data, apply different kinds of analysis approaches to learn something about the patient and the patient's condition. Diagnostics means we're actually trying to make a decision of something that's wrong, and treatment means we're trying to correct. So I'll try to speak in terms of those three categories and show you some of the examples that we have touched on in different ways.

So maybe the one area to talk about in the area of monitoring is actually correcting pectus excavatum with my colleague Mike Harrison at UCSF. So the idea here is you have the sunken chest, congenital defect, and fusion has to be fixed by a surgical procedure. This procedure typically requires you to break the cartilage, open the chest up, and put in this rod and straighten out of the chest over a period of time. It seems to work, but it's painful; and because of the pain, many of the young patients tend to avoid doing this at the right time.

So the idea is can we do this in a different way? So my colleague over the years thought about the idea of let's try to remodel the chest slowly and gradually, and this shows the concept that we have developed at UCSF. So the idea is you actually open the chest up

and put a magnet inside the chest, you close the chest, and then have the kid wear a magnetic brace on the outside, and over time, gradually, the magnetic forces remodel the chest. So you're now doing, instead of trying to fix the chest in one go, you're doing it over the course of months. And this concept has been tried in patients; it has been successful in patients.

But as we do this, a number of questions arise. You know, what are the parameters that are actually made to the right amount of treatment? So how long do you have to wear the brace? You have to wear it 24 hours a day. How should the magnet pull without causing trauma or without being unsafe in other ways? How does the actual body remodel upon exploit of this magnetic field? So I categorized this by a number of questions that can come up from something that's already in the clinic, moving from very much clinical questions all the way to basic science, and as you can see, this can actually then feed back on itself.

So to do this, a few years ago we got involved, and we thought the way to do this was to actually quantify the answers to how hard the magnet should push and how often the child should wear it by putting sensors on the device. So we actually put a strain gauge-based sensor and a temperature sensor, and the temperature sensor on the outside happens to be a very good monitor for compliance. So it just measures if the kid is wearing it or not. If you take it off, it goes to room temperature, that is, close to 37 degrees centigrade. And then by putting this force sensor, we're able to actually monitor how much force the brace is experiencing, and over time, that gives us some knowledge as to what forces are required to remodel. So that could be answering some scientific questions in a systematic way.

So this is an example of the project where you start off with a clinical problem; people have worked on it, and then we bring the smartness that's enabled by sensing

devices. Admittedly, this is not a sophisticated miniaturized sensor, but it's a first pass as to what is possible to validate the concept. And then by validating the concept, we can go work back to make sure that we can actually bring higher resolution sensors, lower power, and the like.

So where is this headed today? So here's actually a patient. As you can see, this is the patient on the left, and this is the implant in the middle and this the external brace. And in this case, it's a boy who wears it for a few hours every day, and what we've been able to do is actually use Bluetooth to send the data through the phone, use the phone as a pass-through to a cloud server and store the data for reviewing by the research group later on.

I know we talk about cybersecurity and the like, but this is a concept of what is possible in the concept with SMART devices. And it's just not about the sensor itself, because that self-enables the information, but it's the other part of it; how do you get the data from the implanted or wearable sensor back to the patient or the physician and maybe even the FDA team that needs it?

So part of what goes with this is a robust data pathway from the sensor back to the patient. And we decided to pick a phone because that's ubiquitous in the patient community. So here I show an iPhone, but we also have an Android version. All right, so this is a project that basically takes the idea of can we start off with an existing device and add smarts to it when it's in the clinic?

The next project I'll show you is some of the work we did -- started at the Cleveland Clinic where we get spine fusion monitoring. And the idea here is to monitor the healing process through microfabricated sensors during the course of fusion. As some of you know, something that's hard to detect, mal-fusion. Or we detect when there are too many problems with the implant itself, implant failure. So the working hypothesis we had at the

time is that over the course of healing, there's a big shift in load from the implant to the fused mass. And if you're able to do this predictably and come up with the signature, you'll be able to predict the likelihood of failure and avoid possibly the need for unnecessary revision surgeries.

We did not stop there, then say let's make a device. We actually had Lisa Ferrara do an in vivo experiment where she took conventional off-the-shelf transducers at the time, put it into a fusion model in goats, as you can see -- the little picture on the top -- put sensors with wires in the fusion mass, and monitor it over a few weeks. And what you'll see in a number of these cases, after the first few -- 5 days, there's actually a change. So something does happen, there's some shift that happens, and we did not conduct the studies sufficiently and rigorously to make the long-term conclusions, but we knew that pressure does matter, and putting a sensor in the fusion mass might have some ability for us to detect fusion condition after the surgery.

So that led us to think about can we use the technology of MEMS to make a wireless, battery-less sensor? Why wireless? Because you want to monitor it after surgery. Why battery-less? Partly because to make it small but also avoid the concerns that may be associated with the toxicity of the battery materials. So we picked the technology of passive circuitry, and we're able to make prototype sensors, and that led to a concept of can we now have a technology to think in terms of in vivo biomechanics? See, if we have a second sensor, maybe not only can we look at fusion mass monitoring, but it will also measure loads, biomechanical loads within bones and tissues and on implants and maybe just not in the spine but in the other areas of musculoskeletal concern.

So here are some examples of some of the simulations work we did. So there's a sensor here that we put into the defect model in the femoral head and simulated walking on a machine. As you can see, the pressure detection actually has a correlation with the

walking motion, and this is being detected through the wireless interface.

Here's another unrelated fracture. So we actually made a fracture model, put a plate and put some sensors underneath it, and what you see on the right-hand side is the graft. So we took a screwdriver and turned it one-quarter turn on each of the screws, and what you're seeing is the change in the readout. So, clearly, the ability to transfuse the signals from the bone to the sensor exists, and then the question comes up: Can we develop the technology to make it more user friendly by having a wireless interface?

This also led to the concept of spine, where we can actually look at variation in the spine, reaction to changes in the intradiscal load. So we actually put sensors in the load in a disc in different locations and manipulated the spine on a machine, and you can see difference of signatures. And we hypothesized that if we're able to do this and we're able to get signals, maybe it's possible to use the loads as a signature for healthy and unhealthy types of biomechanics.

Eventually, we had a concept saying that maybe there's a clinical way to think about this where you could actually use this to diagnose, not monitor only but actually diagnose the degenerative disc disease by taking loads. And now when the sensor is yet to be developed for a second application and we have to work out some of the issues that might be caused by the sensor, the concept is that we'd be able to provide the physician and the surgeon a way to diagnose the status of the patient's spine.

So this leads us to a way to do both monitoring and diagnosis. The hardest one, I think, is treatment. So some of the work I'm doing at UCSF today, again, with my colleague in pediatric surgery, is the idea of a magnetically actuated growth rod. We call it the ROBOImplant, and it's being targeted for both scoliosis as well as limb lengthening, and what you see on the top left-hand side is actually the magnetic rod inside the sheep spine, and on the bottom right is actually an external drive with a controller. And what it does is

as you bring the controller and switch it on, it lengthens the spine ever so -- it lengthens the rod ever so slightly to adjust the biomechanics so the spine, in the case of the scoliosis, would be straightened. And every day you could give a little bit of a dose. And, of course, the next step is you could do this in such a way that it could become completely automated, but I think we're some distance away from that.

So, with this, I'll stop by just giving you a sense for the kinds of projects that can go from monitoring all the way to diagnosis. So thank you.

(Applause.)

DR. GOEL: Thank you, Shuvo Roy. An excellent talk. And as he showed in the slide, our next speaker is Dr. Lisa Ferrara, who was groomed by Dr. Shuvo Roy in spinal fusion technology, and to make some money and make some living, she left academia and started her own companies. But, unfortunately, she was not able to get rid of research aspects, so today we will see the blend of research which she learned at Cleveland Clinic Foundation and the assessment of devices which she has been doing for the past 20-30 years.

So Dr. Lisa Ferrara.

DR. FERRARA: Thank you. Not only was I mentored by Dr. Roy, I was also mentored by Dr. Goel, so I was very, very fortunate. And as I got older, I liked to boss people around, so working device companies, telling them what I think, has kind of just been a natural course for me.

Just my disclosure with respect to the test facility and consulting.

This morning I'm going to talk about the industry concerns and market outlook, and then I'm going to touch upon evaluating SMART ortho technologies, also identifying and addressing the risks and assessing the challenges and the pitfalls.

But I want to start really with defining what innovation is. It's the process of translating an idea or invention into a good or service that creates value for improving the

quality of life and for which consumers will adopt. But also SMART technology, well, what does it stand for? SMART technology is self-monitoring, analysis, reporting technology. Basically, it's technology that's capable to adapt automatically and modify behavior to fit the environment, able to sense the stimuli and the environment and provide that data to analyze.

But when we think about SMART innovation -- and these are questions. When I started with Dr. Roy with this idea about SMART implants and sensors to detect bone healing, we received a lot of these questions. So from an industry perspective, one of the questions is does it offer a solution to a problem that currently does not exist, meaning the solution doesn't exist. Is it superior to other conventional products that do not provide the solutions nor do they address the root cause, i.e., addressing the cause of the pain, the physiological cause of the pain? Is it truly novel, or is it just an incremental change to a device? And is it a technology looking for an application?

So I'm going to use the word "system" today because when we look at implants, it's not just about the implant, and there's a number of SMART ortho implants and tools, but together they work as a system. So when we evaluate, we should evaluate the system.

So there are SMART tools out there now, and it's really an exciting time and, you know, we dabbled with SMART scalpels and microneedles for drug delivery.

SMART implants: As you all know, there's the Verasense knee currently, and we're moving into other areas of implantables.

SMART diagnostics, with respect to the wearables and the lab on a chip. SMART treatments with drug delivery systems.

SMART biomaterials, polymers that have different strain responses. So I always use -- I don't know if you remember Silly Putty. It's a viscoelastic material, but theoretically, it's PDMS. It is a SMART biomaterial. If you pull it fast, what happens? It snaps. If you pull it

slowly, you get a larger deformation. So that truly is a SMART polymer.

And then, of course, SMART design, so implants that are SMART just by their design. And I've dabbled in this area, and we've worked with a lot, and a lot of you have seen them, especially with the manufactured implants and their structures.

But from a market perspective, the outlook is, with the sedentary lifestyles and the poor nutrition, there's a greater prevalence of chronic diseases that will continue to increase. We're all living a lot longer, thank goodness, but we're ending up with an overburdened healthcare system because we do live longer. Therefore, we need to take innovative leaps in medical technology, and this is going to be crucial in the future. Current market developments will lead to patient-specific treatments, and we're already starting to see that with specialized drug plans, etc. And it's logical for the long-term economics, but we do need the acceptance and the adoption of new technologies.

From the industry perspective, and these are only a few of their concerns, it must really be a disruptive and superior technology really for maximum value. Does it offer a superior solution to the patient quality of life? And that's going to increase its adoption.

Overall, it must be safe and effective, and it must work well. Just because something is safe and effective, it's still -- that effective says, okay, it functions as it's intended to, but you really want it to function better than it's intended to. So you try to really strive for that.

It is challenging and costly, not only from the regulatory processes but also from the evaluation, the manufacturing; there's a lot of factors to that. As we know, there are reimbursement challenges post-approval, pricing concerns. Can I recoup my development costs and still remain competitive? And especially with respect to the hospital adoption, the cost and the time to market. And we also need greater user acceptance and adoption to really generate that greater profit to the industry as well.

But the big question is, okay, this is great, but how are we going to evaluate these SMART ortho systems? So here's the 50,000-foot level. First, you need to understand the technology. You need to understand, if you're the developer, everything you can possibly understand about that technology. Develop it, test it, tweak it, test it. And that's a continuing process. Identify those indications and risks, identify them early on, but it's going to continue throughout the lifespan of the product. And also know the environment that you're going to expose this to.

When we talk about testing and evaluating these systems -- and, again, systems, meaning the implant and the tooling, the diagnostic and therapeutic aspects. And I bring them up because often we'll get clients that come in and say, hey, I've got this implant but they ignore the tooling part, and the tooling can sell that product just as much as the implant. You might have the greatest implant in the world, but if your tooling is inadequate, surgeons aren't going to want to use it because there's so many issues with respect to timing and blood loss, etc., that come into play.

There is a lack of current testing, and there's some guidelines for these systems because, as you know, the technology develops at a much faster rate than the test standard. So you have to be a little bit creative here. There's a lack of equipment and resources to evaluate new technologies. And also there are failures. Understanding those failures is just as important as understanding the system and the implants.

So when we're looking at nanoparticulate, for instance, there's a bandwidth. We know nanoparticulate, especially metallic, can be 60 to 100 nm, I believe. And there wasn't equipment years -- recently, years ago, that could actually detect nanoparticulate. We've evolved, and we've got equipment that can now measure it.

Also, SMART implants with the same indications -- when it happens, there's going to be a lot of SMART implants with the same indications. But the way they're SMART, how

they operate in that SMART manner may differ. So it's not going to be a "me too" with the same "me too" type of sensor system; it will be very different. So we're going to have to really think out of the box and design applicable tests perhaps for just that particular SMART system.

So although the implant may be a 510(k) item, that SMART technology that's added to it may be different, and it also increases the risks, the challenges, the tests, the failure modes, the mechanisms, the validation processes, and the regulatory pathway. With that, we've got these new technologies that bring on new challenges. Understand that. What are the new failures, what are the new risks? And, again, it's a longer process, and there will be new regulations. So we really need to think out of the box.

But some of the techniques we can use is to fall back on our technological -- history of technological characteristics. So there's a number of implants and years of research work that have gone on in the medical device industry. Utilize some of these characteristics. Utilize standards from the textile industry. And we spend a lot of our time in this area because we get a lot of novel devices or nuances or additions to implants and their systems where you'll say, okay, I've got this material, but there's not a standard for it. Maybe you'll pull a standard from the textile or from the electronics group or software.

Explore this history of prior approved implants with one or more similar technical characteristics and figure out which ones may apply to really complete that entire picture of the device. So you may be pulling from five different implants or five different types of systems that each have a little bit of an aspect that contribute to that one implant system, SMART implant system that you want to get approved, and use those to get the test guidelines and the methods and clinical aspects of it to really complete that story for your specific device.

So as an example, I took the -- hip implant, conventional, but on the left is -- it can

either be a microcantilever MEMS-based system or a nano. And if you wanted to do something as an example, look at nanoparticulate and perhaps osteolysis starting, you can implant these sensors and this is -- I'm just throwing this one out there along this hip implant.

So although you may assess the implant per the regular 510(k) process, you're not going to assess the sensors part of this. There's going to be a lot more testing you're going to need to do to really evaluate the risks that those sensors may add to this system.

So when you're thinking just about the safety evaluation, again, you've got to fit all these pieces together. You can't just do one test; you can't do just one animal study and go, oh yeah, this is going to address everything. It's really about putting an entire story together, linking everything so that you can complete that story and you develop a SMART system, but you've also evaluated it as a system.

Provide the comprehensive tests for a full safety profile. Some test standards may apply, i.e., just a typical hip implant, you're going to test it in that manner, but you're also going to have new test protocols. You're going to have new risks. Address these risks. You're going to have to validate the electronics, the software, the housing, even the system as a whole really to complete that picture.

So when you address those risks, we know that there's a balance between the safety risk and the clinical need. Greater safety risks exist with greater challenges; therefore, you're going to need a more rigorous regulatory path and more rigorous testing. If the clinical need is great, it's going to have very high value, which means you're going to have to put forth a lot of effort with all of the testing and evaluation. But you may be able to work with the FDA, for instance, to fast-track those technologies depending on that need. Again, we know that the risk assessment continues throughout the product life cycle. And you should, you should always be monitoring such risks and repeating validation tests.

But there's also risks to these SMART systems, things like nano-debris and, you know, we look at abrasion, but nano-debris and electric charge and corrosion and residuals and physiochemical reactions, the dosage and long-term effects of nano-debris. Just because it's small and may be able to be lysed by the cells if it's in large doses, do we know what that effect is on the tissues locally and peripherally? What about the strength of these nanostructures? Is there flaking? Is there delamination? And what happens with the tissues, and can they migrate? What are the effects on cell differentiation? So we're going to have new risks, new failure modes, new challenges, and new regulations.

Know your pitfalls, pitfalls such as unrealistic goals and timelines, inadequate and unrealistic funding. You can't take shortcuts on this. And is it going to cost a bit more for that development? Of course it is. You can't have an inexperienced team. In other words, don't try to save a few dollars because now you'll end up with an inexperienced team; it's going to take a lot longer, and it's going to be painful for you.

Improper animal models: Just because it's a model that's been done or published doesn't make it the right model for your technology, so understand that. Failure to conduct clinically relevant testing. Lack of identifying and understanding the failure modes as well. So really not putting together a comprehensive plan can be detrimental to your device.

The pathway to success: Well, something I thought about for a while now and which I'm glad that we're all here together to really discuss this a bit more is to really apply that team approach. You can have this team of experts interfacing with the FDA; we all work as a team with the seasoned experts and core competencies so that we can bring that good idea and make it a great idea and a valuable technology.

So the evolution of technology and medicine: As we all know, we want to continue to innovate, we want to be the leaders, we want to improve the outcomes, the quality of life and longevity and continue to progress. And we're going to see the good, the bad, and

the ugly, and we learn from that. So our job here is really to minimize the bad and the ugly.

Thank you for your time.

(Applause.)

DR. DMITRIEV: Thank you, Dr. Ferrara.

Our final speaker for this session will be Professor Maharbiz. Professor Maharbiz comes to us from UC Berkeley. And we've heard a great outline of what technology has been available to us and various applications and what could be some of the challenges in addressing the different applications of this technology, but right now let's take an even more open line and look into the future. Professor Maharbiz is well known throughout the world for his focus on the miniaturization of technology. He is one of the inventors of neural dust, and this is extremely miniature ultrasonic interface and interface devices that are used in the body for both sensing and actuation and response. This technology has gained significant interest from DARPA applications and otherwise, so welcome Professor Maharbiz to share his perspective on what the future of SMART implants holds for us.

Dr. Maharbiz.

DR. MAHARBIZ: Hi, everybody. I'm very honored to be asked to speak at this, given that my overlap with orthopedics, of course, is entirely through my collaborators at UCSF. I've had the great pleasure to work with some very amazing people, including Shuvo and many others, some of which will show up in these slides. But it was a little difficult to figure out what to show you, and so I think the way I'll do it -- and there are far more slides here than I'm going to talk to. They're mostly here for people to look at later. But what I want to do is skip through maybe three trees to follow on Mark's analogy, and I think Mark's talk, in fact, was the perfect intro to this. I think the talk dovetails very nicely from what he presented.

What I want to do -- well, okay. So a little bit about me in 20 seconds; otherwise, I'll

run out of time. I build all sorts of gadgets. I like building gadgets, I like building really, really small gadgets, and I like building really, really small gadgets that interface with biology, whether that's for basic science, things that are here, basic cell biology, and understand what we are seeing cells do, all the way to implants. I've had a couple of startup companies, including one that has to do with neural dust, and so I've kind of seen the gamut of all of this. More recently, I've been very heavily invested in the neural space and some of the -- two of the three trees I'm going to talk about are, in fact, applications that come out of neural -- you know, in my mind, to sort of showcase where that field has taken some of these questions given the immense amount of funding and excitement in that area. And then I'll end with a third tree, if you will, that's very specific to the work with UCSF.

So here's what I want to do, very quickly. I want to give an example of work that we did at what we would call the thin film side, and I'll explain what that means for those of you who don't know. And it has a specific message that, I think, has been absorbed maybe by all of the FDA, but certainly through our lenses by a part of the FDA that is looking at the neural device space. And I think it's a very important, very specific message if your -- if this turns out to apply, but I think it will heavily to this field.

The second is a story about how you can really miniaturize devices in ways you wouldn't have thought possible before and put them very deep, and I'll do that very quickly, making the point that although it's called neural dust, the applications are turning out to be very broad and well outside of the neural space.

And then the third one is an example, then, of taking technology and specifically trying to look at something in bone fracture, for example. And what I'll do, as we near the end of that third vignette, is to come back and say think about the first two and now think about what we saw for the bone work. Imagine now where this is going. And hopefully

that will be sort of a useful set of stories.

Okay, so neural applications right now are -- they're in a gold rush. Arguably, they're at the peak of the hype cycle, and everybody knows the sort of hockey stick model and so everyone's -- maybe if you're a cynic you're expecting, you know, people to start roller-coasting down. But there is a lot of excitement, there's a lot of excitement all across from industry to academia. And what's interesting is that behind all the excitement there's also the realization that nothing we put into people's bodies to interface with the nervous system has a chance of surviving for 40 years. That's an extremely strong assertion, but it's actually true. The only place where you could have a tiny bit of argument are for very large, mature derivatives of common -- of, you know, cans, very mature cans like you would use in a pacemaker. But pretty much everything else, and certainly all the things that catch people's attention in the media, have no hope of surviving for extended periods of time. Period.

And so the question is why, and what is everybody going to do about it if we envision a future where we're putting this into healthier and healthier people?

So the story is actually very, very complex for, you know, what this is. It's a story that, you know, requires hours in a whole symposium to do justice and have a lot of academic and industry people get into nice arguments. But the high-level 30,000-foot view is that it involves at least two different directions of aggression that give rise to the failure modes. So one of them is that your implant is going to aggress the tissue due to its size, its mechanical properties, the fact that they're usually tethered to something and so on and so forth.

The other side of the coin is that you, being a very big, you know, sort of complex bag of salt water, will aggress the materials very strongly. And the analogy I use, that when I say it this way and everybody gets it, especially engineers, is if I told you you were going to

design the state-of-the-art chip and throw it in the ocean and let it sit there for 40 years and still work the whole time, everyone would think that, automatically, it's preposterous, but for some reason nobody thought that was preposterous, you know, when you start thinking about these very small neural implants and the same thing happens.

So those two things are -- you know, those two observations which are in themselves very complex are part of what drives the story. So the two trees I'm going to show you extremely quickly are kind of looking at both of those directions. It has become sort of part of the field, of the matrix of the field, now that people do admit that making extremely small implants would matter.

So if you look at the right, this is a classic result. That scale bar, if memory serves, is 100 μ, and the blue is glial staining. So this has been inserted into the cortex, this is the structure that's been inserted into the cortex to record, and you can see how much encapsulation there is. What you don't see, unless you have a very good projector or you know what you're looking at, is that right next to the left is a tiny, little square, and that was a much smaller implant that was put in there, and not only this paper, but several papers have shown that there is a site threshold below which you get almost no encapsulation and the body almost doesn't care, and there's a long story for why that may be.

So where this field was going or is going, continues to go, is to make smaller and smaller objects, to make them wireless. So the top right there, you have a variety -- or the right side of the screen, you have a variety of attempts to make smaller and smaller things that can record and stimulate the nervous system. They use the latest electronics, smaller and smaller chips, tricks from MEMS techniques and so forth, to try to go from the two pictures you see on the top left, where actual patients are wearing what are maybe, you know, the gold standard 10 years ago or 12 years ago, and now we're trying to make them smaller and smaller. So keep that in the back of your head.

And also keep in the back of your head that there are fundamental physics entitlements. You know, at the end of the day, physics still rules. And so bottom left you can see, those of you that are engineers, that there are limits to how much space things can actually take, must take, to operate and how much power they must consume.

Okay, so given that I have 7 minutes left, now we're going to super fast.

So we looked at the material space and looked specifically at a particular solution for making very, very long-lasting electrodes. Now, I'm not going to tell the -- the whole point is not to do a power talk on how great silicon carbide is; it's to show you what you have to do to convince yourself a little bit that this might be a way to go.

So you develop an entire technology that is thin film, okay? And I'll explain why in a minute. In other words, this is not common manufacturing of the big, you know, classical type. This is depositing using chemical vapor deposition and, you know, physical vapor deposition and classic techniques out of nanofabrication, micron-thick films that are going to be stacked up together to give you, say, an electrical interface that you can then connect to a chip to do something it tells you, take a recording, do a simulation, take data, and so on. The key is that you want all of this stuff to last for a very long time.

Okay, so you want to do this. You end up having to build -- and this is directly out of -- this is out of one of the dissertations of my students, but it was copied directly from work at the FDA. So the FDA, I think, in this regard has been ahead of the curve, looking carefully about as implants get so small that they're no longer canned, they can't be laser-welded, hermetically sealed ceramic or platinum -- or titanium, rather, cans. How do you validate that those, you know, 5 µ films are going to last in the body? You can't do accelerated lifetime testing in real living objects, organisms, obviously. And this is a really hard problem.

So my sort of take-home message from this little tree is that as things get smaller,

thin film technology is going to take a very front and center role, and we do not have, no matter what anybody tells you, I think, a great set of solutions all the way from testing, you know, to lifetime estimation to even on the technology stack.

So we built these very high-temperature aggressive hydrogen peroxide chambers that, like I said, were copied from publications coming out of the FDA, and then we sit there and put these things through a barrage of tests, which in some cases we invented or a colleague of ours invented a month before we were doing the study, so this is moving very fast. We were looking at how much leakage there is to an insulator while it's being aggressed and so on. So this is a field that's sort of rapidly evolving to try to get a sense of how you score thin film. So this is all, again, not for you to really absorb in 5 minutes, but it's for you to go back and look. That's why I put the data.

You have to then do a lot of impedance and electrical characterization. That changes with time. Nobody really understands, in many cases for these materials, how that does, so you do your best, and you try to do it before and after and during certain tests. But in the end, the gold standard is you have to put it in an animal, and you have to test, and then you have this sort of very difficult question of how long are you going to put it in there. You know, you can't wait 20 years before something develops. So what is the best way that you can score all this work you did on the chemical side and on the reliability side purely in vitro? How do you then try to map it to in vivo? This is a big deal, and I think that in the neural space it's been taken pretty seriously.

Okay. This, I'm going to go even faster. Neural dust is an idea that was driven by the dream of having very, very small implants, like I said, but really small. So the neural dust question was if I told you I wanted an implant that was 500 µ on a side or smaller, could you build such a thing and put it deep in the body; is it physically possible? And you find that if you try to do this with wireless radiofrequency electromagnetics and your goal is to build

things that are smaller than a millimeter cubed and deep in your body, say in your liver, somewhere deep inside in your torso, you find that radiofrequency solutions fail because you're a bag of salt water, and we can get into the why. What works very nicely, and what kicked off this whole sort of neural dust meme, is the observation that if I build an implant that has a crystal that's responsive to ultrasound, I can, in fact, use ultrasound to power it and that implant, by changing little impedance changes on the crystal, can reflect back different amounts of energy and encode digital information. So now I can build an entire powering and up/downlink communication system entirely from -- on an ultrasound modality, and this happens to scale extremely well. So you're going to see a future in the next decade of implants that are a size scale that were, you know, before, the size of a single vial in an implant. And this is moving pretty fast in industry as well.

I will skip all of this. This is the neural dust being, you know, inserted into nerves and, you know, you find that you can talk to them and take data that's as good as wired. So you can ask me about it later.

And to kind of get to the closed-loop part of this, today we have, you know, matured beyond that where these dust motes can actually stimulate nerves, so now you can do closed loop, you can record and stimulate at approximately the same scale, and now it's just going to -- you know, in the next few years now, it's just going to be an order of technology development. There's no doubt, really, that you're going to end up with, you know, in the hundreds of micron size implants that can do, you know, very useful therapies in the peripheral and eventually the central nervous system.

Lastly, with 1 minute -- this is good because I can skid into home base right as the clock runs out. We were very curious as to whether there's any of this we could bring to bear to looking at a problem like bone fracture monitoring, and this is, as I mentioned, done with fantastic colleagues at UCSF. What we did -- I'll skip this. All of you probably, or at

least a fraction, a good fraction of you know what fractures are and why they're important, but what we wanted to do was ask could I leave something in the fracture gap that was so small and could take some data to tell us how well something is healed with the idea that these things would be integrated -- let me skip ahead. This is all for you to look at later, but with the idea that this could be integrated with, say, typical bone screws or bone plate technology or in some future -- literally, just put into the gap even if you're not getting a plate. The point of the project, specifically, was to ask whether we could take electrical data, electrical impedance spectroscopy data, and did that data correlate with the different stages of bone healing, and the answer is it turns out it does. And these implants can be so small that, you know, they essentially would have little to no effect if you left them in there, and in another, you know, incarnation you can see at the top right, that bone plate is actually instrumented. You can kind of see the traces running along the top of the plate. You could just integrate it straight into the plate.

So, you know, what are my closing thoughts, because I have 12 seconds left and I want to kind of stimulate and sort of provoke, and then in the panel discussion, we can revisit this. The number of sensors that have been developed for other things, you know, non-orthopedic uses over the last 40 years, as Mark said, is absolutely just astounding. It's a universe of methods by which you can -- and technologies and chemistries by which you can take data out and put it back in. I think what we're seeing now is that the technology has matured, and there have been specific technology leaps that are allowing us to truly envision very, very small, completely untethered things put everywhere in the body.

So the neural dust story, as an example, is moving well beyond recording from nerves or stimulating nerves for therapies on that -- you know, on that scale to looking at, you know, diagnostics, internal diagnostics, in a way that wearables could never do. So you're really thinking about fitting your liver or fitting your kidney. And this is getting, you

know, funding. This is becoming very, very -- of great interest in the commercial sector.

So I know I went very fast, and I didn't quite do justice to all of these topics, but it was really just to sort of throw buckshot out there and get a sense -- give you a sense of lots of things that are going on. Thank you for putting up with my speech at a million miles an hour, and I'll go take a seat.

(Applause.)

DR. DMITRIEV: Thank you, Dr. Maharbiz.

Well, we have about 35 minutes for discussion, and I'm going to join the panel at the table. We encourage you to come up to the microphones and also engage in this conversation. We have folks online, and at this point, I think, how many attendees do we have currently logged in?

UNIDENTIFIED SPEAKER: One hundred and eighty. A hundred and eighty.

DR. DMITRIEV: A hundred and eighty attendees are also listening to us online, and the room is almost full. So this has definitely turned out to be a great start to the meeting. We have now laid the foundation for this technology, and I open up the panel session. For us to actually hear the voices and the recording online, please press the microphone button as you speak.

DR. GOEL: Please introduce yourself before you ask the question.

So, Hassan, go ahead.

DR. SERHAN: Hassan Serhan, DePuy Synthes Spine.

I have a couple of questions, actually, regarding the sensors. Lisa, you talked about the validation of these sensors. There's a transient use, like if you're looking for a fusion, it takes a very short period of time before you achieve that. Other sensors, we talk about like infection and long-term wear and wear debris.

How do you validate that? I mean, in your car, you go and inspect it every year and

get a sticker. How do you validate that the sensors are still working for a prolonged period of time? The fusion, we can check it off in a year of time. How do you go about the wear debris? I mean, that's a challenge for all of us. I just want to put it on the table here.

DR. DMITRIEV: And maybe if I could add to that question. As a matter of fact, that's not only about the wear debris, but if we're talking about the different modes of application, certainly for shorter-term use, that would be a one-and-done type of sensor reliability aspect. But if we're thinking about more arthroplasty type of systems that have the expectation to perform adequately and accurately for at least 10 years, and there are systems out there and certainly more and more development goes into the biomaterials to enhance the durability of these devices beyond a decade, how do we keep track and ensure that the sensors that are still outputting the data continue to output the accurate data so that it is reliable and trustworthy and we're not getting basically sort of a -- just erroneous information?

DR. FERRARA: Okay, I'll start. That's a huge challenge, and that's kind of where I was going with this. A lot of this is going to be independent, but it's also going to involve bringing in other experts, electrical engineers, because short term obviously is going to be a little bit easier to address, and we may just start with short term because we know long term, and that was part of the problem with my dissertation work too. It doesn't last a long time -- it wasn't a wireless system -- but the wires break. The human body is an incredibly harsh environment.

So how do we simulate that environment? We're going to have to get very, very, very creative with respect to can we produce similar flow patterns, can we produce similar fluids to induce that harsh environment, but that's one piece of it. So it is going to be a phased-step process. We can't just jump in and go, all right, it's going to be 10 years because you'll fail right now, at this point. Right now we still have to address the short

term, and we're just going to have to be very creative, and we have to work with a team and not just within our small population.

DR. SERHAN: Like with packaging, we do accelerated, you know, aging. Is there an accelerated process or test method for these prolonged period of time sensors that we could shorten our test duration and address it within 6-month or 3-month aging versus a lifetime of 10 years or 20 years?

DR. FERRARA: I would say, right now, anybody -- I would say no right now, but --

DR. THOMSON: Well, a couple of comments, I guess. The first is pretty fundamental, which I'd say is don't put it inside the body if you can put it outside the body.

DR. FERRARA: Um-hum.

DR. THOMSON: Accessibility is one thing, and I think we're assuming a lot of sensors need to be implanted into the body. We should always stand back and say what are we really trying to measure here? And is it a short-term thing; is it a long-term thing? Recovery to normal gait, for example, you know, probably doesn't need a long-term implantable sensor. So if it can be done with a wearable, then use a wearable. And gait analysis, for example, could be done pretty well with a phone, so you may not need a wearable even.

The other thing is there's new and there's new to us, and in terms of sensor technologies, there are -- you know, they're new in the medical space, but you mentioned car sensors, for example, they're designed to, you know, last 10 years or more. Plate sensors that are used in planes in high risk/high failure, high risk of failure environments, those things are tested extremely well. So there are very well-established test protocols and sensor protocols for accelerated life testing. We're just not used to them in the healthcare space.

DR. FERRARA: If I could make one more comment, too, is -- you know, we're

focusing everything around sensors. That increases our challenge with respect to putting these sensors on implants and in the body. But we may want to talk about SMART designs that can give the same effects. So something we've been working on is looking at micromechanics of implants and being able to measure that, but those micromechanics, now with the advent of additive manufacturing, which has been around in aerospace and they've got all of their protocols in place, it's new to us. Yet, we can use that to start to create designs that respond in a SMART manner without the sensor technology.

DR. ROY: Can I add one more thing? So a good down-to-earth example is your airbag deployment sensor that's in your car. Each of those sensors self-check and self-calibrate. Every time you turn on your engine, it tests for that. So with the new technologies that are coming down the pike, you can envision building those kinds of tests and calibration into the healthcare sensors.

DR. MAHARBIZ: So I'll add a couple of thoughts just because I really appreciate your question. There is no accelerated lifetime testing that properly simulates what goes on in the body and even in very narrow parts of that. There have been some recent attempts. Like I said, notably from the FDA, the groups trying to develop these new testing paradigms are pretty clever, that looks at oxidative stress and temperature and so on. But there isn't.

But I will say something that I think may be, you know, relevant to this talk, is that -- or this workshop. There is a deep competence in some of these matters, in companies that have historically looked at electrical interfaces. So, you know, I don't want to do specific names, right, but you all know there are very large companies that have been building these types of devices at a larger scale, and my interactions with the technical part of those companies has always been extremely -- they're very impressive, the good ones.

And there's a galaxy -- the other thing, I think, everyone should realize is that for every one of those large companies, there's a galaxy of startups around them, moving

around, right, that they eat or don't eat or compete or whatever. I've been very impressed with the amount of mature know-how built up in industry and perspective in substantive companies. I can't speak at all to orthopedic implants, I know nothing about them, but those companies, they do know quite a bit about it, and I think that what you're going to see, and what you are seeing, is the fusion of the type of accelerated testing that we get in the semiconductor industry, so on and so forth, the auto industry. And these kind of companies are sort of increasingly coming together and then building more sophisticated models and sort of mockups for this because there isn't -- but there isn't -- the short answer to your question is there isn't -- there's no oven I can throw something in and it will do everything that you would do to an implant.

DR. DMITRIEV: Thank you. And we have a couple of folks at the microphones. I just wanted to point out one thing for posterity's sake, and Dr. Margerrison has shown on his slide, but I wanted to retrieve the disclaimer, that the discussion of any technology or specific devices at this forum, we encourage the scientific dialogue, but it does not constitute endorsement by the FDA. So, with that, please.

DR. WEBSTER: Excellent. So Tom Webster from Northeastern University and a member of the CDMI. So this is excellent. Thank you all for your presentations.

So I guess I have a question about what is it you think we should be measuring in the body. And I'm a big fan of implantable devices because I -- implantable sensors and systems, to use Lisa's term, because I think we need things that respond to what we're sensing. You know, we see a lot of interest and a lot of people asking questions about is the particular antibiotic that's prescribed working? Is the anti-inflammatory agent reducing chronic inflammation? So those kinds of questions and the ability for an implant to respond to that medication, which is different for patients, is very important.

So I think, what is it that would be, in your minds, ideal for us to measure? You

know, we heard a lot about pressure and I think pressure, probably with sensors, is the farthest along, implantable pressure transducers, but perhaps the time it takes to measure changes in pressure to indicate bone formation or osteochondral formation is too long. And then you could think, I think, of course, about chemical -- measuring different growth factors or cytokines surrounding the implant. But as we know, you know, I think oxygen increase occurs for many different scenarios, not just healing, but infection increase of oxygen levels can occur. And maybe it's a combination of all of these things, but I'd love to hear some insight. You know, as an engineer, what is it should I design to measure?

DR. ALLEN: So maybe my first comment would be maybe we're not the people to ask. Maybe the physicians are the ones to ask. But I can tell you some secondhand things that I've heard from some physician colleagues of mine. One of them seems to be that radiographically, it's very difficult to tell the integrity of some of these metallic repairs. You know, screws come loose, but you can't quite tell on a radiograph. Patients come in and complain, oh, my implant hurts. They get an x-ray; you can't see anything wrong. Perhaps a screw is coming out; perhaps an infection is occurring. So I think that there are things we could measure that monitor the integrity of repairs, for example.

DR. DMITRIEV: And I think our clinical session will address some of the questions that you raised, and absolutely, we will give the voice to our clinicians to understand what it is that they and the patients need to have a better understanding of on the quantitative fashioning or quantitative manner, I guess, in order to enhance recovery and performance of devices.

DR. GOEL: I'd like to raise another question in relation to Tom's question that is addressed. That is, if I listen to all the talks you have presented, it looks like fracture healing sensor is very close to application. There are a number of different ways to figure out the fracture healing. It could be used in spine; it could be used in fracture of the tibia

and other things. But as you know, the load on the structure is complex. How many devices are you going to put, where are you going to put those devices, and will those be assembled at the time of surgery by the surgeon, or will it be a plate coming from the company readymade and put it there? Because the application is going to be different from patient to patient.

DR. THOMSON: Maybe just to add one thing. This will refer back to something I mentioned in my presentation, which is, I think, real lifestyle and sort of patient-focused metrics are important, in addition to the ones that you listed, and I think those really kind of broaden out our perspective on what we're trying to achieve. And even as we measure things which are kind of more traditionally medical, I think there's a chance to put those in the context of somebody's life as well. So if we're measuring fracture healing, it's good to measure it in the context of the person's life, lifestyle, activities, mobility, and so on so that we can gather, I think, a lot of learnings around what really impacts, and not just measure but to learn as well, and to guide.

DR. FERRARA: I think that's the key point, and I'm still going to take us back to is it a technology looking for an application? So I think the very first thing we need to do, and then that's what Tom was asking, what are we going to measure? First, identify the problem. Can we develop a SMART technology which is a better way to address that problem, versus the reverse with, okay, what do you measure, because there's going to be a lot of different things we're going to want to measure to -- for each patient as well.

So even thinking about the fracture healing, we have to think about, well, what are the problems? It's different for young patients than it is for older patients with fracture healing and compromised bone. So we really need to sit down, and again as a team, and say, well, what are the problems and what are the large problems that could really -- technologies such as this could really change the lifestyles, the longevity, and the quality of

life for these patients. That's the very first thing we need to do.

DR. ROY: So I have a slightly different take on that, Lisa, and I think maybe the question from the gentleman there before, you know, what should we measure? And maybe looking back, I should say why would you need to just go after pressure? It turns out if we want to go after pressure, it's not because that was what everybody wanted, but is the easiest one to implement in a short period of time. A lot of people want to measure biochemical parameters, and at the time when I looked at the field, what jumped out at me was the 35/40-year effort in developing a long-term glucose sensor, which today is still a challenge. So we can take and say we want to make biochemical parameters, but chances are we're going down a research path and not a patient implementation path.

So when we went back 10-15 years ago, what we saw was that 30 years of pressure sensor development that had happened starting in the late '60s, we had a technology that was very robust. There was one device that was going through clinical trials from a company, and that was going to go the heart, and those were the first wireless MEMS device for health application in 25 years. And then you look at all the interest from the physician side who said I want to make chemical parameters, and then we just looked and said there's no way to build long-term sensors for that. The best we can do is a chemical sensor for just a few days.

So I think one of the things we want to do, as engineers, if we want to take a perspective, is can we find the right surrogate? And we consider time pressure sensing or mechanical load sensor is the right or the best surrogate we could get.

Then I think you can just stratify the problem by saying what's the time frame? If it's only a couple of days, great, we can make you chemical sensors. If it's 6 months, it's not a chemical sensor, and this is an emerging technology that's not invasive, and I think we need to decide what time frame we're going to go after and then see if there's a right surrogate

that's already established or can be ready to put into practice.

DR. DMITRIEV: Question in the middle?

MS. SAAIBI: Sure. Ana Saaibi from OrthoSensor.

I wanted to ask more of a general question and see your thoughts on it. You're all mentioning innovative methods of testing new devices. What has been your experience with the FDA actually presenting this -- by industry presenting the innovative methods of testing the devices, and what has been your interaction with the FDA accepting this innovation testing?

DR. MAHARBIZ: I'll take a quick stab at that. Like I said, those of us that follow the neural side of it have been -- I mean, I've been pretty impressed. I mean, the FDA has been proactive about understanding it, not just from an academic side, but from -- you know, from a regulatory or approval perspective to sort of have a sensibility to the -- a responsible sensibility to the rapidity with which things are happening. That's our perspective.

So another hat I wear is I have a venture capital-funded implant company and that -- you know, we're going through all of that, you know, IDE stuff with consultants and the usual stuff, and I have to say, often in the academic side, I think, probably wisely, because it sort of preloads the right set of expectations, everyone fears the FDA, right? That's like the bogeyman that's waiting for you. And yet in all of the actual times where the sort of rubber has hit the road, it's actually been a very positive experience either as a spectator, like reading those papers and then using them, or through interaction.

DR. FERRARA: It's been a very positive experience because I'm living the other side of this now where I'm working as that liaison between the devices and the FDA, and I enjoy coming to the FDA because you sit with the group, and most of the time there are added tests that are very different, they're not standardized, but you're also getting their feedback. They're seeing so much more of some of the issues that are happening that you

have no knowledge of. So to work as a group with them and to be able to ask questions and pose here's what we did, here's what we're thinking of doing, it's very, very positive.

DR. MARGERRISON: I'd just like to say, on behalf of FDA, thank you for the lovely comments.

(Laughter.)

DR. MARGERRISON: But also that there's a couple of important points. I think today is very much the start of a dialogue in this particular part of the industry. Obviously, the orthopedics industry is mature; it's been around for a long time. I think today can be considered the start of what are we going to do next? Have we really reached the design limit of existing materials? Maybe. What's coming next? We need to know that as much as everyone else in the room because then, as Lisa said, we can work together.

Part of our function is actually to be able to develop standardized test methods which makes it easier for the whole community of industry and also easier for Mark's reviewers, because the last thing they want is 14 submissions with 14 different test methods. It takes longer for all of us that way. So the more we can do that, then the better for all of us, I think. So I'd like to encourage everybody to continue that dialogue. Even if it's very, very early stages, you can reach out to people like Anton and myself, and we'll talk any time.

DR. DMITRIEV: We have a couple of questions in the room.

Dr. Yates.

DR. YATES: Yeah. Dr. Yates, UPMC.

Size matters, and nanotechnology is very exciting because it's measuring size, and my question revolves around accelerated testing for safety. You know, it may be one thing for a device to fail after 4 years because of being in the ocean, so to speak, but it's another thing if it harms the patient or it doesn't harm the patient. And in that sense of harm, it

strikes me that one of the slides was very impressive of how a really small blue dot was entirely encapsulated and yet the other one was not.

Cannot the safety aspect of it be accelerated by looking at the finite amount of potential byproducts either through corrosion or breakage or whatever happens at the nanomolecular level? Can that not be then tested in terms of what becomes safely encapsulated in an animal model in a way that's linear, that you increase the size such that you see what does not get encapsulated and put away by the body as opposed to what gets captured or put away and doesn't cause harm? And in that sense, you would accelerate and go to the worst possible point and find out whether or not that encapsulation occurs and that it's safely encapsulated with collagen and isn't going to cause long-term harm.

And I don't know, has that kind of testing been done with the -- again, I think there's only a finite number of different byproducts that you could evolve out that dissolution of the components, and it strikes me that it's potentially a way of getting around the -- at least the one safety question as to what happens long term in a faster way.

DR. MAHARBIZ: Yeah, so I'll take a stab at that. So some of it has been done, although there's a lot -- I have to unpack your question. So a lot has been done, or some, let's say some has been done at least in two areas. There have been studies both in the brain and then outside, you know, elsewhere in the body to try to get at the notion of how size affects fibrosis. There have been more limited studies looking at how tethering -- so, for example, the thing I showed was, in fact, not -- say, a cube. You know, the blue square you're alluding to, it's actually a shank that's 2 mm long. It's a needle, and it's stuck straight down into your cortex for recording, and that's the cross-section of that.

There's two parts to your question, so I think you focused mostly on the dissolution, so I'll do justice to that in a minute. But you have to remember, also, that even the question of size is actually rather complex because -- let me give you one simple example.

In cortex, when you go puncture something, the more, you know, innervated something is, the more vascularized it is. So what you're doing is pop, pop, pop, pop, pop, pop. You're popping capillaries all the way down, right? When you make something that's 4 µ in size, there's some very, very nice data out of UT Austin, very recent, that -- you know, let's say a carbon fiber, just to pick something -- will actually sneak around those things because it's so -- you know, it's just enough that it will pop around and then -- so there's a very complex interplay between the material choices you make and the consequences that then have downstream consequences on what happens over the next 6 months. I think anybody that -- the clinicians that I've talked to and everybody here who is a clinician knows that just from -- if you've ever done, you know, surgery, the technique matters. What you use to suture matters, where you put it matters; all that stuff matters. So that's the size part of it. It has been looked at. It's been looked at pretty reasonably across a few fields, again neural.

The dissolution part of it has been looked at more extensively recently because there has been -- first of all, it had been looked at originally. There are classic studies looking at what gets eluted out from, you know, the standard palette of implants. More recently, there's been a subfield in our community looking at purposely dissolving things, and so then they had to look very carefully, and I think one of the eye-opening parts of that work is that many more things than we think of dissolve, right? So you think, oh, I'm going to put a piece of silicon -- that doesn't dissolve, right? Well, no, silicon dissolves, and it happens to dissolve at a very slow rate, but that becomes meaningful to your point as the surface area to volume ratio increases and you're talking about a thing that's 100 µ in size, right?

The last thing I'll say before I'll be quiet is that you say that there's -- I think I heard you say -- and if you didn't, I apologize. I think you said, oh, there's a limited number, you know, of these materials. That's actually misleading. The consequence of allowing

sophisticated electronics of the integrated circuit variety of chips, the consequence of letting chips into the body is that chips are made with an interesting palette of materials, none of which necessarily are going to cause a huge amount of concern, but you have to look at them. You can't just claim if I put an ASIC in your body and it dissolves, everything will be fine. There's all sorts of polymers in there. There's metals, a variety of different metals. And so, you know, people have looked at this, but you also have to take that -- you have to look at that carefully. Where did you park that implant? How close is it to something? Do you care about the elution rate? As the copper comes off, do you care about that? So those things, I think, have been looked at a little bit. That probably is going to be more deserving of attention if, in fact, we believe that those chips are going to be closer and closer to tissue to prevent harm.

The classic solution to doing this was to put it in a can, right? The classic implant can. The way you deal with this, if you're bigger than 5 mm in size, is you just put it in a titanium can and you laser-weld it, you backfill, and you say the body will never see what's inside that can, no matter what happens. If you start moving into a world where that's less and less sure, then you better be a little more careful about what you're putting in, to your point.

DR. ALLEN: I think we also have an opportunity -- I agree with everything that was just said, but I think we have an opportunity in this space to worry a little bit less about the size, because if we're going to be putting in a hip replacement that's this big, then the sensor being this big or this big may not matter as much. But smaller is probably still better, regardless. Or, alternatively, we might take the opportunity to stud this hip implant with a thousand sensors, and then we're back to the same, you know, size issue. But at least here we might be able to get away with slightly larger devices, sensors, as adjuncts to the main therapeutic repair.

DR. DMITRIEV: Thank you. We have a couple of questions from our regulatory colleagues, and I would love to hear from them, so Brent, if you would like to start?

MR. SHOWALTER: Yeah. As he mentioned, I'm Brent Showalter. I work at the FDA.

My question is with regards to MR safety. So a lot of these -- I mean, kind of by definition, these devices have circuits in them, and they have other things that are not going to necessarily react well to an MR environment. So in lot of cases you might be trading off the increased sensor capabilities of the device itself with the loss of the very standard diagnostic capabilities that you might have in MR. So I was wondering if you could discuss, one, that tradeoff but also discuss mitigation efforts to make -- you know, there are ways to make your devices MR safe. I was wondering if you could discuss that a little bit.

DR. ALLEN: Well, I think maybe starting with the simplest devices, as Dr. Roy mentioned, there are passive devices that are MR safe or can be made MR safe. But, of course, there's a tradeoff between that and functionality, right? There are some things that people who try to do -- lots of RF communication used that may or may not be compatible with MR, such as, you know, putting big magnetic slabs inside of the devices to facilitate transmission, and there you're relying on more advanced approaches to communication or even doing away with RF altogether, and moving to things like ultrasound, as we heard today, might be ways that we can address this.

I think what I have been more afraid of is not so much incompatibility but that the sensors now cast a shadow or an image or hide something, an aura about them that prevents you from seeing other things within the imaging modality. And so I think we have to worry about that piece as well. I don't think the chips themselves contain lots of magnetic components or anything like that.

MR. GOODE: John Goode, FDA. I'm with the Orthopedic Devices Branch. I've been here about 20 years, and I just want to put a plug in for standardization. That word has

come up several times today. I've been part of two standardization groups: an ASTM F04, which is on testing and materials; a Society International group, they have over 900 members. I'm the chairman of the arthroplasty subcommittee, so we talk about all arthroplasty type of devices. There's also a similar group in osteosynthesis. So I know we're being fed a lot of information today. To me, it's like drinking from a fire hydrant, and I think my brain is already full. And so if you're looking for other groups to help work out some of these questions that have been asked today, I encourage the involvement in standardization. We meet twice a year at ASTM, and we have -- in arthroplasty, we have 200 members; we have people who make presentations at these meetings, we discuss these questions, and we try to write standards to help address them.

I'm also the chairman of ISO/TC 150, so implants for surgery, ISO chairman for the past 7 years. And, again, that's another group to work with, depending on whether you're trying to market in the U.S., market internationally, that can weigh into it. But what you get there are people involved in industry, academia, test houses, all of the different stakeholders, as well as government stakeholders that can help discuss and work out and sort out these questions in a more systematic way, a longer-term way than maybe what the information that we can discuss and disseminate today would be.

So, again, I encourage setting up new groups or collaborations with ASTM. Now, I know everybody's money is tight and you can't send everybody to every meeting, and I understand that, so we try to have Webexes, WebEx communication at the standards meetings, so we might have 30, 40 people on the phone as well. So if your university does not value standards and is not going to send you to a standards meeting -- I hear that very often -- call us up, be on the phone for a couple hours, and get your questions answered and your -- maybe you can even make a presentation over the WebEx as well.

So the question becomes have you been involved in any standards? Maybe there

are different standards organizations that I'm not a part of that you guys are, but I am part of groups that you've mentioned with respect to fracture healing or arthroplasty or these type of devices and maybe joint working groups need to be set up to figure out and give some perspective on these issues. To me, the valuable thing about standards is you hear and listen and learn from other people's bad experiences, and you cannot just come to the FDA to tell about your device, but you could find out about somebody else tried something and it didn't work or it did work and how to expedite this whole process. So any comments about standards, I'd love to hear.

DR. FERRARA: And that was excellent -- thanks, John -- because I'm involved in a lot of the standards as well. I think the one piece that's missing with the standards is that clinical aspect. There are a few clinicians and surgeons that attend the meetings, but we definitely need more there so that we can complete the picture, even with the standards. And it provides education to them with respect to really what it takes for the testing and the evaluation and getting these things through the FDA as well.

DR. DMITRIEV: This is an excellent point, both Lisa and John. John, thanks for bringing this up.

We're out of time, so we have to wrap this up. This dialogue, I think, can continue for hours on. But at the same time, before we close, I have one -- just to point out one thing, and there's the reason why we brought the experts from a diverse community of engineering into the room to talk about orthopedic implants or orthopedic sensor technology, SMART technology in orthopedics, and that's because we are in a very early or nascent stage in orthopedics. As Professor Maharbiz mentioned, there are a myriad of sensors developed in other applications and even other healthcare sectors. Yet, in orthopedics, we're still talking about, you know, pressure sensors and maybe string gauges.

So I'm wondering, is there a role for the community to come together through the

standards organizations to start coming up with a glossary of terms and definitions, at least for us to start putting the foundation of how we approach developing the testing methodologies, how we start evaluating the risks the different sensors introduce into the space? And can we leverage what has been learned in other areas and industries to bring orthopedics, if not up to speed, I wouldn't want to use that term, but basically in line with other communities? Maybe everyone could comment just for a few seconds and then we will conclude.

DR. MAHARBIZ: I would say yes.

(Laughter.)

DR. FERRARA: I would, too, because that's where you're going to get the best outcome when you pull all of it back together and we're all speaking the same language.

DR. ROY: I think the place to look at in the clinical area is probably the area of cardiovascular devices because a lot more has warranted implanted devices. Then, outside the clinical area, I would look at aerospace and automotive because there has been a lot of work in the standardization and also how to bring protocols together for testing.

DR. ALLEN: Yes, I would add my agreement and maybe a comment, which is that although it is probably true that there is no one test that can mimic the acceleration that we need in the body, there may be subtests that can get at -- with, you know, reasonable accuracy or maybe not, I don't know, but at least we should start to think about what subtests might be appropriate for orthopedics.

DR. THOMSON: I guess I'd also agree. I think, as you've said it, is the right way, Anton. I don't think this field is mature enough to have standards today, but I think it's certainly at the stage where we should start thinking about what information we need to gather to get to those standards.

DR. MARGERRISON: I agree as well. The analogy I might draw is maybe on the

in vitro diagnostic side, where traditionally awhile ago we might test one analyte or two. Now we're using whole chips and using next-generation sequencing to get a much bigger profile. And I think that will be the case here as well, but we're trying to measure oxygen or pressure. One day we're going to be measuring many, many more things, which is why we've got to have ongoing standards communities and an ongoing dialogue.

DR. LOTZ: Sure, thanks. I'll just add one comment about the standards in terms of the minimum detectable change that these sensors are going to provide, and that really needs to be put in context of the minimum clinically important difference. And so I think this next session is really going to help us think about how these sensors are envisioned to be used, and that is critically important for us to think about what are the data and the quality of the data these sensors are meant to provide.

DR. GOEL: I'm sure we can close the session because I agree with you all.

(Laughter.)

DR. DMITRIEV: Well, thank you very much.

DR. GOEL: Thanks to all the speakers for keeping on time, all the panelists for the excellent discussion. Please keep sending us the comments and your questions. I'm sure you'll put something together.

DR. DMITRIEV: Absolutely. As part of the outcomes -- and you will hear this throughout the day -- part of the outcomes of this workshop, we would like to collect the feedback and the comments and sort of synergize the discussions that take place throughout the day so we're able to actually initiate laying down the foundation and the definitions through either a white paper type of form or peer-reviewed publications or something a little bit more specific to the FDA as well. Thank you, all.

DR. GOEL: Thank you.

(Applause.)

DR. DMITRIEV: We will now take a 15-minute break and reconvene with our clinical session.

(Off the record at 10:31 a.m.)

(On the record at 10:46 a.m.)

DR. WEBER: Good morning, this is Dr. Steve Weber from FDA, Department of Orthopedic Devices, and we're going to try and go ahead and start with the clinical session. Moderating with me is Dr. Adolph Yates, who is an orthopedic surgeon and associate professor from UPMC, and he's a fellow Hopkins physician, as I am, and is associate professor and vice chair for quality management within UPMC Department of Orthopedic Surgery and has served on a number of device panels for FDA. So, with that, I'm going to let Dr. Yates do the introductions for this exciting seminar.

DR. YATES: Good morning. If I could have your attention, we're going to start the session, and if you have conversations, if you want to take them outside, that will be great, but otherwise we're going to try to start here.

Our first speaker is going to be Dr. Joseph Kvedar. He's the vice president of Connected Health and a member of Partners HealthCare, a professor at Harvard Medical School. He has been heavily involved in new models of healthcare delivery, authoring two books on the subject. At Partners Connected Health, he is leveraging technology to better manage across the spectrum of healthcare.

Dr. Kvedar.

DR. KVEDAR: About 3½ -- can we hear?

DR. YATES: Yeah.

DR. KVEDAR: All right, I'm going to have lean over. About 3½ years ago, I was driving home. I often get inspired when I'm driving and listening to NPR, and I heard a stat that by 2020 -- so not long from now, and it's actually tracking -- by 2020 we'll have over 20

billion everyday objects that we normally think of as inanimate, will be connected, will have sensors, will communicate with themselves and with the environment. And, of course, that's what we now call the internet of Things. At the time that was somewhat of a newer concept, at least in the media, and I was struck by that stat. Now again, this is pre-Nest thermostat. A lot has happened in just that period of time. But for me, of course, I went directly to how will this affect the way we provide care? And it was so inspiring to me that it ended up becoming the subject matter for a book that we published just about a year later. So this book came out in October of 2015, and it's a journey into how this idea of connected devices will really transform the care we deliver.

One of the interesting things about having published a book and then spoken about it and heard about people's reactions to it now for 2½ years is that a lot of what we talked about has actually already come true, which is really remarkable when you consider that we thought it was the future we were predicting, and I guess we were, but we weren't off by much in terms of time.

And so in order to get a sense of how this world will evolve, we cast the first chapter as a journey into the future. So now we're going into the future even from here 2 or 3 years, and I have just agreed to participate in a program by my employer, teaching hospitals in the Partners HealthCare system in Boston, and it's a tradeoff. So I get to be followed in my life by a virtual coach called Sam, and Sam is informed by all of the private and personal data that I'm giving off, as some of you will understand the term "digital exhaust." It's really everything that comes off my wearables, my mobile devices, etc. So Sam can have access to all that and, using that information, guide me to a healthier state.

So you might ask why on earth did you sign up for that? And the answer is, well, I got a premium discount, and by that time, which again is not that far away now, we will have figured out just how much value this kind of thing can add in terms of lowering

healthcare costs.

The other part of the story that's happening in the future here, in the first chapter of the book, is that my daughter is getting married in a few months, and so that's really the motivator for Sam to keep reminding me to make healthy choices. So he wants me not to show up at my daughter's wedding looking like this, really, right? But rather more James Bond-like, like that. Sam can get me there because he has access to all of this information. Now, these are all screens from my mobile device taken not long ago and therefore they're all -- this part of the future is already here. These are screens of various wearables or mobile apps, things that I use to track my health.

And, again, Sam has access to all of that so he can do things like remind me that I'm only two blocks -- my office -- from Boston Sports Club and that I could actually take up swimming again. The last time I swam for exercise was when I was in medical school, but Sam reminds me that I could do that, that actually there are four or five people in my Facebook friends that also are members there. There are times when we could meet for a swim. So things like that, that degree of personalization. Or I'm out for a walk at lunch, and Sam reminds me not to probably go get that chocolate chip cookie that's on my mind because he sees I'm headed towards the bakery.

Now, at the end of this day we describe in the book, my daughter chimes in with a message and says, Dad, I'm so appreciative that you didn't get that cookie for lunch, and I think swimming would be great for you, and you're going to look great at my wedding.

So that's the kind of environment that I'm building out with this internet of healthy things. And as I said, a lot of those snippets of that are already now happening, so that future is not far off, but there are missing pieces, and that's really what I wanted to talk to you about today. And I will bring it into the context of orthopedic implants, I promise. I just wanted to start with a very, very sort of high-level view of the power that these

internet of Things sensors can bring to the way we deliver care and talk about health.

Now, I divide the landscape up into these three areas. So there's the idea about data aggregation, normalization, the sensors themselves, the things, if you will, in the internet of healthy things, so there's a bit about that. There is the middle part, the analytics. Once I get all of that information -- and there's a lot of it, as you know, coming off of these sensors -- how do I create a unique persona? How do I make sense about it? And then, finally, how do I engage each one of you in a very personal journey to improve your health? We'll talk about all three of those here briefly.

So, first, data aggregation and normalization. And, again, this is about how the sensors themselves interact. It's a little bit easier to go back for a moment to the story about screens that I showed a moment ago and just remind everyone that although these days I can show my Fitbit data, which is an approximation of calories expended, on the same screen with my smart scale data, if I have a Nokia smart scale, which I've had for now almost 10 years -- and I can also, if I'm meticulous and put my calories that I take in into an app like MyFitnessPal, I can display that; I can display all those numbers on the same screen now.

That's convenient technology because of APIs and OAuth and technologies like that. But they don't really tell a story; they don't relate to one another. They should tell a story. I should be able to predict one from the other two, and we can't do that yet, and that's what I mean by normalization, and that's a critical piece to getting this set of technologies into widespread use in predicting healthy behavior and how to get there.

Now, in the world of orthopedic sensors, I'm not an orthopedist, so I can only imagine. But look at the ideas. The ideas, of course, of detecting early evidence of infection, the ideas of detecting new insights into joint stress, these were talked about in the panel just previously.

Real-time evidence of how you're doing in your rehab. Anyone who's been involved in either personally rehabbing an orthopedic injury or is involved in the profession as a physical therapist or a PM&R specialist knows just how terrible we are at following the directions around our rehab. And if you can imagine the sensor giving that feedback loop to the clinician that allows them to know exactly how you're doing and just how powerful that would be in changing the way we rehab, I think that's an enormous, enormous opportunity. But in order to get there, we have to do a couple of things still. And, again, one of them is this normalization. We have to be able to display those data in some way or -- I shouldn't say display -- we have to be able to capture and normalize those data coming from those various sensors so that they actually tell a story, that they relate to one another, that I can predict one from two or three other variables. That's a really important thing for all of the innovators in the audience to sort out.

And then integration. Now, we do some integration into our electronic health record where I work. We can see, for instance, your weight data; we can see your blood pressure data, if we choose to ask you to submit it. It's all done wirelessly, so we've achieved that, but it isn't integrated deeply into the record, and the reason for that is because of things like policies around whether a human being has to sign off on data before it gets to be part of the record and things like that. So we have a ways to go on the integration conversation as well.

Now, the fun -- maybe funnest part for some of you is the analytics. That term itself is even dated since I published this book because now AI is the term, right? If you're a startup and you don't have AI, you kind of can't visit the VCs anymore. It's really become this sort of powerful buzzword in the industry.

But if you think back to all the data that Sam had about me and yet Sam could say I think you're headed to the bakery after lunch there and you probably don't want to get the

cookie, that level of sophistication does not exist in today's Chatbox and other solutions, and it's because we have a ways to go in the analytics space.

To illustrate where we might get to, I want to tell you a story of some work that we did in our own group. We have an innovation team of about 45 individuals where I work that work for me, and they do a lot of industry collaboration, they do a lot of technology validation, design, etc., and one of the projects we came up with -- this one actually was grant funded before we ended up getting a technology partner for it, so we started on grant resources, and the idea we came up with was we asked the question could we change the behavior of individuals without bringing a human being into the conversation, could we motivate people to change a health behavior?

We chose Type 2 diabetes as a substrate, and we chose walking as the behavior we wanted to change. And the very first iteration of this was very simple. We sent people a daily text message that was informed by four variables. The first variable was their actual walking behavior as measured by a wearable. The second was -- and these are not really in order because I think the second one is a more powerful predictor, which is how motivated are you to change your behavior. And we asked people five questions routinely in this process, and we just based on those five short questions can get a sense of where they are in their journey of being motivated to change their behavior. The other two are a little bit of location data, nothing as sophisticated as what Sam knew about me but a little bit of location-based data, and weather.

And when you take those four variables on a daily basis and you put them into a very, very -- actually, for today's technology, simple analytic engine and you fire off a message each day that is personalized and customized, it turns out that after 6 months of that, people with Type 2 diabetes and that intervention had improved their diabetes as well as if they took metformin, so as good as a drug. And their, of course, activity level went up

commensurately as well, compared to a control group.

So we thought that was pretty interesting because we could change behavior without a human being, right? And then Samsung came in and they're -- now they've licensed the IP, and we're working with them on doing something that's much more powerful here.

So it seems as though we can get there. It seems as though we can get to a level of analytics sophistication and personalization where we can motivate people to change their behavior, but again, we have a ways to go. And when I get back to my thinking about SMART implants, I think about all the other stuff around you that's going to inform how powerful that data will become, things like, again, if you're in a rehab scenario, knowing what your GPS tracking actually is.

Or we know, for instance, it's very well correlated that the number of outbound messages you send, not the content, but the number of texts, emails, etc., is highly correlated with your mood. So if you can imagine someone's not very active in their rehab and your system knows that they're not sending a lot of outbound messages, maybe they're just depressed, maybe it's not because they're not rehabbing well. That kind of nuance, when you combine that with the sensor-level information you're going to get from these SMART implants, that's when I think we can really start to think about a transformative healthcare environment.

And finally engagement. So it's perhaps not something, when we think about things like orthopedic implants, that comes to mind right away. But the real power of these tools is in how we engage people with all that data. So if I know everything about you and I can make that very personalized persona but I can't get your attention to change your behavior, it's not really very interesting. And we have a chapter in the book around this and it's -- we've broken our engagement thought into three strategies and three tactics. I'll share a

little bit of each now.

So the strategies, and, again, these sort of follow the story that I told earlier; they were reflected in the story.

The first is make it about life. If I want to motivate you to do a change, and I say if you don't change, you're going to have a heart attack in 10 years. We've probably figured out by now that's not very motivating. So that's why, in my story, it was about my daughter's wedding, much more powerful to make it about something near term that I need to achieve.

The second is personalization, really critical. And, again, every mobile app developed for now on the planet knows this, that the more personalized, the more focused any given interaction on your mobile device is, the more likely you are to engage with it. And that's why Sam was so personalized. That's why when I told the story about diabetes, we think the reason that was so powerful is because of the personalization.

And then finally social. Now, at the end of my story that I told earlier, my daughter chimes in with all of this positive reinforcement because I'm working hard to lose a little bit of weight and fit into my tux. That's social, and you can map that to so many different things. And, again, every developer now that develops a mobile device, or rather a mobile app, will bring in some sort of social interaction because that's a really powerful influence.

The tactics are subliminal messaging. It turns out this is another kind of a fun story, but it turns out that you'll do better if you put your healthcare message under something that's a little more exciting. We're competing with things like Snapchat and Instagram. Health is either reminding you that you're sick or it's hard, so it's not very interesting compared to those other stimuli.

A very quick story: I'm a dermatologist by training. One of my residents came in a few years back and said what if we sent a text message to people; do you think they would

put their sunscreen on? And I said I don't know. Well, let's design a study and try. So we did, and with a daily reminder to put on sunscreen, people put their sunscreen on 60% more often than people in a control group, just a daily text message reminder. The fun part of the story, though, is when we went back and asked them, it was like -- because now, if we were designing it, we'd never design it that way. We know so much more that the same message every day is not powerful. Well, someone in the team that I didn't know about, so much smarter than me, had put a daily weather report in that text message, and this was during the days before we had smartphone apps, so people were getting a weather report. So we went back and asked the subjects in the intervention group what was so special about text messages for sunscreen? And they said I didn't think much about the sunscreen, but I enjoyed getting the weather report. That's what I mean by subliminal messaging.

Unpredictable rewards is another one. It's just you keep looking because you don't want to miss something.

And then sentinel effect is a variation on social. The idea there is that there are certain people in your life that you care what they think about you more than others, and usually your doctor or the doctor's nurses, someone in that practice, counts as one of those individuals. It might be your mom, it might be your spouse, right, it might be your best friend as well. You don't want to look bad in front of them. And so we used that in our app design for healthcare apps, because if we can get people's attention and they know they're being watched by the healthcare provider, they behave differently, and that's a very, very powerful stimulus.

So let's think about it for a minute. Now, the goal here is to maximum all of this, right? Why did I get invited here? Because the goal is to maximize the value of these sensors that you're talking about, these SMART implants, the internet of healthy things. The trouble is we tend to focus on technology as opposed to transformation. The whole

reason that I've been telling these stories is to try to get you to think about not just the details of the tech, which I know you're all much better at than I am, but how can we use it to think differently about care, how we combine it with other data streams to really reach something that's much more powerful. I think if we can get there, we can actually achieve that goal of maximizing the value of these whole systems and really transform the way we deliver care.

So it's really about consumer-centric design, again, fitting into everyday life, personalization as I talked about, really powerful, and the sentinel effect.

I think if we can use those sensors, combine them with other data streams, get really, really sharp analytics, and then start to think about how we use those to maximize behavior change, we can achieve this goal of having a much, much more powerful healthcare delivery system. I suspect it will be at lower cost with improved outcomes. And it's exciting to be a part of that. I'm sure you think it is too.

These are all my contact information. It's been a pleasure to come and talk to you about this, and I'll look forward to hearing the rest of the talks in the session. Thank you.

(Applause.)

DR. YATES: A mechanical point. We're going to ask the speakers to have a seat in the front, and then after we have the Fireside Chat with our patients, they're going to come back up for the moderated session for the panel.

Our next speaker is Dr. Aenor Sawyer, Director, UCSF, of the Skeletal Health Service and Health Innovations Technology in Ortho. She has two decades of experience in health technology innovation in both device and digital health sectors. Her innovation work is focused on developing methodologies to understand individualized function in real-life settings.

Dr. Sawyer.

DR. SAWYER: Great. I really want to thank the organizers for this opportunity, and to the attendees, and I'm looking forward to the conversation after this. I think there will be great synergy between what I'm going to say and what Joe just said.

No disclosures here that have any conflict.

So I want to talk a little bit because I was asked to talk about the clinical impact of the sensor technology in orthopedics. I think there are some movements afoot that are important to address when we contextualize where we are right now in healthcare and the transformation. One is this shift in this focus now towards precision medicine, which sort of juxtaposes two things: the person, the individualized approach, but also population health. And I think that's a really important complicated scenario to hold together, but we can do it because we have this fantastic opportunity now that we've never had before, which is a tremendous amount of ubiquitous data sources. It's a headache, but it's also an opportunity.

So we have the genome, the phenome, and the microbiome all the way out to what I now call the phoneme, which is the consumer analytics that we're picking up out of our individual devices now. And somewhere in there are biosensors, which we have, I think, a great opportunity to expand upon.

Another movement afoot is that we have more the empowered and engaged patient and patients who have access to information, whether sometimes they can contextualize it and sometimes they can't, but it's very important because we know now that engaged patients and activated patients have better outcomes. This is another shift that I think is important in what we're talking about.

We also have a movement that's sort of institutionalized now within our organizations to gather patient-generated health data. And it really is important for us to understand better what's happening with patients, what are the influences on them, how

are they responding to it in their real lives, and it's what I call their life flow. And so far, our clinical tests and our artificial settings where we bring them to isn't giving us a good sense of what's really happening in their real lives.

So I think it's very important for us, when we look at the patient-generated data, to go beyond PRO or just subjective data and look for how we can bring in quantified, not just qualified, information or quantitative data along with qualitative. We've got some good structure building for this from the ONC, and I think we should look at this framework as we're building out our understanding of implantable sensors as well, and how we'll incorporate it into the patient-generated health data.

But the individual, to me, still remains an untapped source for physiologic, biomechanic, biometric data. And some people feel like we've come a long way with the wearables, and I think we have to a certain extent, but there's such a limitation with them still, with them not being well validated, and oftentimes there's such a drop-off rate. By 6 months, most -- at least half are in the drawer for most people. And it also requires active collection, so the patient has to do something; they've got to remember to charge it and put it back on, and usually they're getting information from fragmented sources.

And the main thing is something I've now nicknamed the value-to-nuance ratio, and if that value-to-nuance ratio is not right, you're just not going to stick with it. Joe is a highly motivated individual, but most people, most humans tend to -- unless they get something out of it in the way they need it, with a very low nuance, will not stick with something.

So we're moving, though, fortunately into a realm where we can shift from just the wearable sensors. We do need them, but how do we move beyond that into SMART implants? And this is a nice article that I wanted to point out by Andreu-Perez, and it's really moving from wearable sensors to SMART implants to pervasive and personalized healthcare, and it's a convergence over the last three generations of sensor technology plus

intelligence. And this has been addressed in many talks today, so I won't spend a lot of time on it.

But I think it's exciting to look across the top, from our first wearable sensors in braces all the way across to programmable sensors that we were applying to people to measure smartphones, and now we're getting into some implantables in certain parts of healthcare. And in parallel to that is the ambient intelligence we're getting from environmental sensors, location sensors, etc., that we can intersect with that, and then, of course, all the supercomputing that's happening as well.

So I'm going to start with human implantable microchips. And this was something that was interesting to me because we know about marine animal trackers and our own pet trackers and our asset trackers. I didn't realize there was a burgeoning industry of human trackers, implantable human trackers, but the FDA knew about it, and in 2004 they actually put an opinion out. So did the AMA in 2007. Unfortunately, that same year in 2007, there started being reports around tumors maybe being associated with these chips in animals. That's still in big debate.

But all that to be said, this is happening, and I think it's important that we know about it. Perhaps there are some things we can learn about it, but it's really important to know that the technology has moved, the DIY movement has moved, the patients' -- people's curiosity has moved. So these things are actually being injected in people, and mostly they're being used as a convenience to activate something that you would either type in a password for or have some clearance for.

So in communities like Sweden, they're even talking about using it to board trains. Most people are using them to open the door to their house or control their phone or use it as a work idea, etc. And I'm not promoting it. By the way, that's your surgeon if you decide to get one of these done. But I think we should look at the industry and follow it and find

out what's happening with it, especially from the safety standpoint.

But using it for a patient's records was an idea that the American Medical Association had, and I think if that advanced in a way that was safe and reasonable, I think that is something for us to think about.

So talking about medical implants or devices, I think it's really important that we think about some of the criteria, and this has been said in several different ways today, but we really need certain components, the signal detection, the processing, the transfer, the power requirement, biocompatibility, longevity, reliability, and precision. And I think, for most of the things that we think about for implants that are going to be giving data, we should be able to send data as well, and as often as possible, create an active system or a closed-loop system. And I think it's very, very important to know that the SMART devices will also be serving an audit trail for us in terms of understanding how are those devices functioning, not just how is the patient functioning.

Again, from the same article I referred to earlier, this is a really nice overview of medical implants and SMART implants that have been going on for years, and it's so interesting that such a huge number of them have to do with function, and that is something that we understand so little of, how people function in their real lives. I have the background as a PT, and so it's particularly interesting, but if you look at these, MSK is addressed in many of these, and it's really because we're trying to get at how do people function.

So starting not in ortho, but just to give an example of a few other industries that have already worked on this and specialties. Again, this was mentioned earlier, this is basically looking at intraocular pressure and glaucoma. These are other contact lenses, SMART lenses. Google actually looked at glucose in tears, and they have teamed up. Also , now Sony and Samsung are actually building AI capabilities out of contact lenses.

This is, again, cochlear implants and going into the idea of active or closed loop, cochlear implants that self-adjust. Hearing aids often do this now if you go into a room, and it will automatically set for the tones the way that you've done it over and over. And these cochlear implants are really interesting because they have been around for a very long time, and I think each of these that have been in place for a while, we should look at and learn what we can from them. The same thing with pacemakers, they were actually introduced in the '50s. But each of these on this page not just give information and report it out, but they actually create a closed-loop function locally, which is really important, and that involves edge analytics, and I think that's a really important concept that we now have at our fingertips. Another is, of course, the glucose monitors, and this is a delivery device as well as just a measuring device.

I think this one's actually particularly interesting in that you can put the leads near where the epileptic activity is, and as the activity increases, you can create stimulation that tends to ablate or minimize the seizure and preemptively decrease the number of seizures that people are having, and this one has been shown to be very effective. And I think, for us, if we're talking about measuring something that's happening in a joint, for instance, an infection, is there some sort of a signal? Could it be an electrical signal, for instance, or a change in pH that we could create that would minimize that risk of infection?

So why orthopedic implants? First of all, we have got to figure out how to minimize the costs of these implants. It's a $30 billion industry right now, and it's expected to go up to $40 billion within the next year.

So it's really extraordinary, and I think one of the things that affects that is the fact that these implants, as many as are being put in, they don't actually have a very long lifespan. They do in my colleague's hand, Dr. Bini, who's going to speak next, but by and large, most of these implants fail after 15 years and for various reasons: wear, loosening,

mal-alignment, etc. But that is actually adding to the cost of these implants and adding to the cost to the healthcare system of these implants. So I think we need to do all that we can to figure out can we predict perhaps, can we pick up early on ones that are likely to fail and create some sort of an intervention?

And so I'm going to give examples of some ortho ones that I think we might not have heard today. I'll skip over any that we've already addressed, but most of them you'll see are still in research mode. I thought this was a really interesting project that was done, again, a research project where they did put sensors in devices, so they did hip, they did shoulder, they did spine, and across all of them they created a large database, and this is actually a very good resource and anyone can access these datasets. And they also compared them to videos of ADLs, or activities of daily living, so they could see when the highest forces were and what they correlated to in that person's life. So I thought this was a really powerful database we should be looking at.

Again, another one that was used just in research mode, but looking at stresses placed on the tibial component of another total knee arthroplasty. These were put in a select number of subjects, quite a bit of information was learned, but it hasn't gone to commercialization yet.

Another one for total knee arthroplasty. And, again, in Dr. Bini's hands, he may not need all these fancy tools, but it seems to be an area where there is a real problem that seems to want to be addressed by having direct measurement.

So balancing of the ligaments is really important; it's one of the things that causes failure. So this is a put-in-and-take-out sensor. It's not left in at this point, although some people are trying to design one that can be left in, and it's really about balancing that ligament gap.

This is another one. This came out of a Swiss organization, research organization.

They're looking at combining sensor signals from the prosthesis to outward-sensing devices and then integrating that more broadly, like Dr. Kvedar talked about, into a broader network and into an app and then giving the patient feedback in terms of loads, activity, types of loads they should and shouldn't be doing at that time.

Again, more sensors. And this is in the components themselves. None of these are in commercialization yet and so -- or in standard of care yet, so just showing them, that these are being tested.

The loosening one we talked a little bit about, the hip loosening one. Sorry, maybe that will come next.

But the other one is temperature, and this was very interesting to me when I was reading about this one. It turns out that temperature alone can be a predictor for failure or loosening, depending on what time or period in maturation of that implant being ingrown. But one thing that causes the temperature to go up is certain kinds of exercise and activities and physical therapy. And so this was a really interesting concept. I thought, first, they were going to be going after infection, but it was actually loosening in this study.

There are others that look at loosening from a different way, where they put a ball in the top of the stem and they pass a wand over it with an acoustic sound and causes a vibration, and when that varies from baseline, that is an indicator of potential loosening.

Again, shoulder measurement systems looking at contact forces. These are all very interesting from a research standpoint but haven't moved into any standard of care.

The spine example we heard about earlier with the growing rods, that is being used clinically. These rods and these measurement systems are -- they are products, but they are mostly in research mode right now, and I don't know of anyone who's using these routinely at this point, but someone else in the audience may.

And then the Ortho-tag is actually interesting in that it's to be device agnostic, and

it's a sensor that's meant to attach to any implant supposedly and can give information in several different parameters. And this one is also still just coming up.

I popped this one in. This is a disc, and I put this one in just because I think we have to be careful of technology over reason. I don't know where this company stands right now -- I haven't been able to locate them again -- but their concept was that when the loads on the disc, this implanted disc, were out of range for what they thought was appropriate, a beep would go off, and I could imagine that that, from a user interface mechanism, is probably not going to last very long. You could imagine this happening at very inconvenient times.

So this is just for us to keep in mind the whole picture. This slide is just information and sending information out.

So we have the opportunity, we have demonstrations already of using SMART implants for clinical impact across a broad variety of areas in orthopedics, at least in the research mode. So, again, always the test is scale and implementation into practice.

But one thing I want us to keep in mind is making sure we're doing this in an affordable way. Unfortunately, I think there are sensors -- very, very basic sensors -- that can give us information about force, pressure, temperature, pH, even presence of antigens, and sometimes we go to the most fancy, but I think we should keep ourselves to trying to hold a cost down when we're looking at these. I think there's so much information to gain. At some point we could demonstrate ROI with increased cost, but we've got to make sure that we're holding ourselves to that standard.

We need to look at these criteria, I think, for moving forward. We need low-power consumption, so long battery life, high reliability, and safety monitoring features. Really as simple as possible, miniature as possible. And the key thing, I think, is what Dr. Kvedar spoke to earlier is we need to intersect this data stream with the other critical data streams

that we have, and we need to actually contextualize that information and turn it into actionable insight. So link it with potentially wearables -- validated wearables -- the new brand of multiparametric and biometric sensing technologies that are coming out, even the medical grade, but in-the-home type devices that we're using to help assess and give feedback to patients and are typical devices. So if we're going to bring these things into the suite of a tapestry of information about patients, we need to hold ourselves to a strong interoperability standard.

And this is just an example of a company that is a device company who's looking at creating a full suite of sensor technology from the implant all the way out to the wearables.

So we really have got to hold ourselves to the standard of interoperability and how are we going to leverage that data and what data is going to be meaningful so we can get to this place of informed health, the right information at the right instance to get the right outcome. This will allow us a paradigm shift, and this was also spoken about earlier.

We need to get away from relying on just subjective -- or if it's objective -- late, late findings of problems, particularly when we have implanted devices. The findings come to us late if we're looking for objective signs of it.

And the missed opportunity of understanding the loads in real-life settings and then also avoiding the episodic or fragmented monitoring that we're doing of patients now when we just bring them into or setting for that information and shift over to contextualize actionable insights.

I was also asked how would clinicians play a role in this, so I throw out a challenge to my clinical friends. If you're putting something on or in a patient, ask yourself what information you might want to know back that would help you optimize that patient across time and what information could be gleaned from the device that's actually in your hands.

And for the FDA, I would -- I wasn't asked to give information to the FDA, but I just

wanted to say one thing is I actually feel like it's time for us now to even break down silos within the FDA, because when you're talking about interoperability and looking at the health sphere of a person, we need to break down whether it's a device or it's software or hardware or it's data -- it's big data analytics -- because all of those are going to come into play to better understanding the individual.

Thank you very much to the organizers and my colleagues.

(Applause.)

DR. YATES: Our next speaker is Dr. Stefano Bini, Professor of Orthopaedic Surgery at the University of California and an old friend of mine through the American Association of Hip and Knee Surgeons, where we've collaborated on multiple projects. Dr. Bini specializes in hip and knee replacement and is the founder and chair of the Digital Orthopaedics Conference, San Francisco, also known as DOCSF. Current research interests include quantifying the impact of digital health on orthopedic care delivery, changing management strategies in healthcare, and improving the results of total joint surgery.

Dr. Bini.

DR. BINI: Thank you. And, again, thanks to the organizers and a quick second to again commend the FDA for creating this event, for reaching out to both consumers and the patients who are here in the audience and industry, to create a colloquium, a discussion around this opportunity that we have before us.

I was tasked with looking at how a surgeon could handle information and how it would benefit our practice. You will hear some recurring themes between the last two speakers, I'm sure, and the next one, which hopefully will actually make the conversation more pointed.

These are my disclosures, and none actually impact the current environment.

I want to show this video because it is of the AC72. These boats are extraordinary;

they're 72 feet long, they're 13 stories tall, they're about 7 tons. They go 55 miles an hour in 20 mile-an-hour winds, and they have over 300 sensors on board collecting 30,000 data points per second, which are being fed back to a team onshore that then optimizes the ship for the next day's races, as well as the captain.

Compare that to my clinic. So that was 4 years ago, by the way, 2013. An amazing time, an amazing race. Greatest comeback in history. But this patient comes to my office and says I have a painful total knee 3 weeks out from surgery. Well, how many sensors do I have available? I've got my hands, I've got my experience, I've got the patient's information, but fortunately in this particular patient, she was also part of a study, and she was actually wearing three sensors that she had been wearing the whole time. So to this patient, I said hold on a second, we're all worried about infection, a big red hot swollen knee, but I notice you're one of our trial patients; do you mind if I take a look at your Fitbit, which was one of the three sensors she was wearing, and she had done, I kid you not, by 2:00 p.m. that day, 3 weeks out from surgery, 11,000 steps. I didn't have to do anything more; I knew what the problem was.

Now, I would like to have that more. We have, as Aenor pointed out so beautifully, a plethora of sensors that are being put into the community, and although it is true that most people do put them in the drawer after 6 months, that is rapidly changing as interfaces are creating more useful data.

And in other areas outside of healthcare, this, of course, is athletics. Pro athletes are being tracked and monitored like crazy and creating graphs like this that are being used by their trainers to decide whether or not they're ready to go back to the field or the court.

So what do sensors do? At the end of the day, it's just simply a way to create a feedback loop. So what's the value of a feedback loop? It's tied to four things in my mind: its accuracy, its relevance, its timeliness, and whether or not you can use the data. How

usable is it? What's the UI you're faced with?

Now, the feedback loop for medicine can be used by surgeons but, yes, also the provider that could be an extender of the surgeon. It could also be the insurance system. The same data could be used by the patient or maybe the caregiver, the aunt, the uncle, the son, the daughter, or the payer or the insurer or the government or, in the future, none of those, but really it's an AI engine with little machine-learning algorithms making decisions directly from that data.

So if we have that kind of dataset? How could it be used by a surgeon? So let's break it down into three areas: well, the preoperative, one intraoperative, and one postoperative. And let's make a path to look at some of the more uncomfortable areas where this data could be used.

So preoperative feedback loop, the time before surgery, the time during which the patient is being evaluated by the surgeon to consider whether or not they should have surgery, where we are looking at data to manage risk. Especially today with the new payment paradigms, it actually is an onus that's being put back on the clinicians to some degree.

We want to optimize outcomes. We'd like to make sure that if we have some data, it can optimize the surgical indications. Is this the right operation for this patient? But at some point, if we have the right dataset, we should be able to define this for this patient.

It would also allow us to prepare patients. Today we ask our patients to please stop smoking, to maybe do some exercise or lose some weight. We're relying on some data points that come back to the clinic. Get a urine test; we'll get it 3 or 4 days later, and we'll find out, but why can't we monitor these things in real time? So these are ways that we can use the data to manage our patients and our decision making ahead of time.

Another area that we don't tend to think about too much, but it's not as sexy but

there's a ton of money in it, is surgical coordination. So RFID tags or the implants or ability to track where these devices are, how sterile a tray is before it comes into the operating room are all going to be particularly useful to help us to optimize the cost of care. So these are areas in the preoperative sphere that we could use sensors as surgeons.

In the intraoperative sphere, we've heard a lot about it already. Clearly, there are two kinds of feedback loops that I think are useful to us. One is -- I put it in the bucket of evolutionary -- they're helping us improve current existing technologies similar to pressure sensors that help us to balance a knee. You may have seen this grasper that has an optic sensor that looks ahead of the device to see if there's a vessel deep in that scar tissue to help you avoid cutting it. I consider these exceptionally useful. Maybe the cost-to-benefit ratio needs to be defined, but nevertheless, they're evolutionary.

But there's some amazing stuff that you've seen already in the last couple of lectures on the revolutionary side to acknowledge the tools that we've never had before that enable us to do things we never even conceived of before. These are biodegradable sensors. They could be nanosensors; they could be elasticized devices that can create pressure points and the like that we have not had the opportunity to use in the past and will change the way we think about surgery.

And then there's patient care tools. And we sort of dance around the issue, but I want to tell you, I'd love to have a sensor that sits in the wound and measures the bacterial count during surgery. Six, seven hours of surgery, you can't help but contaminate that space, and it would be nice to know whether or not it's still contaminated. I can take the sensor out. For those who are worried about these things staying inside you too long, don't worry about it; there's lots of ways we can use chemical sensors, as surgeons, that don't necessarily need to stay in the body.

And it would be inappropriate to not talk about sensors in the context of robotics.

So robots are really nothing more than a sensor coupled to an actuator, and today, robotics still requires a third sensor, the human, to oversee the work of the robots. And you can see that the growth, expected growth of robotics in our world is going to increase. It's not as fast as maybe some of the other technologies, largely because the cost is not likely to come down anytime soon, but there are enabling technologies and how they enable us -- these sensors enable surgeons to do things we couldn't do before. Take the example of the radical prostatectomy; it's a perfect example. It's how the da Vinci robot got its start and why it's 85% or more of the current prosthetic market. Previously, a radical prostatectomy was an extremely painful dissection. Now this is done with minimal impact to the patients in outpatient surgery. So where robotics can help us the most, and sensors associated with those robotics, would be to take us to places we couldn't go before.

The other image there is of a flexible surgical tool that actually goes into the lungs, into the small space of the lungs that you can't access without cutting through the lung, and that's never a good idea.

Now, this is perhaps to some a more uncomfortable space. The same data points that are being collected to help you optimize the surgical care can also be used to see and evaluate the surgeons themselves. Now, we know we have in cars already -- many of the better cars have the ability to track whether or not the driver is falling asleep. And when those surgeons get tired, so will there be sensors that will help to see if we need to break?

How about surgical evaluation? The same sensors measuring whether or not your knee is going imbalanced can also test whether or not you do a pretty good job the first time around. That's not very comfortable for us to think about that we're being evaluated at the same time, but I think, for the consumer, it's actually quite a nice idea. It could be used for quality monitoring. It could be used for recertification purposes. It could also be used for medical/legal. So the reuse of this data, once it's out there, once it's created,

definitely does create some challenges for the surgeons as well.

The postoperative sphere is one that we've all discussed or talked about a great deal, and that is how to use feedback loops to monitor and track the results of surgery. Clearly, we've heard about the use of sensors to identify surgical complications. In our world, typically, this is device failure, device debonding from the bone or device infection.

But there are other interesting ways that we, as surgeons, could use to track these implants. Not just early warning systems so it's before, contextually before, it fails. If I've known, if I've tracked 200 implants that have failed, I might be able to find that there's some data that predicts failure pretty well ahead of time. And so then I can take that dataset and say by the way, Mr. Smith, your implant will fail unless you stop playing singles tennis, unless you don't -- you know, you lose the 100 pounds you put on in the last 6 months.

And there's also a possibility that we can start thinking about warranties so that if you have data from a device like the one that Aenor presented and I'm showing you here as well, that says, hey, listen, you're loading it within parameters, there's a warranty with that. If you go off parameters, we no longer certify it.

And just a moment. This particular dataset that Aenor pointed out is a publicly available dataset, I did use for a study, and what happened was that the loading parameters that were identified by this in vivo device are very different from those that have been used in the past for all the studies that were submitted to the FDA use-for-wear testing, and there were some very -- so my point is that even this was indeed a very important study -- it was done 2009, I believe -- that actually changed the way we think about loading within implants.

So other postoperative feedback loops are of great interest to us, which is how do you track patient results? So this is a study that was done by the CDMI, and there's

Mr. Piccolo, who's going to be our audience -- be one of our patients later on today, and he was 1 of 15 patients that completed a dataset. Now look at the data streams. There are 53 data streams coming in, 326,000 data points total. To this dataset, which is a very structured dataset, we added unstructured data, the entire H&P, imaging reports, and then we collected PRO data.

So as far as looking at single data points and using them to predict outcomes -- this is relatively interesting -- these are step points, and you can see that the patients do well in the middle, a nice progression of their recovery, but the patients who didn't do well didn't have that progression. So you can start seeing how this data could be useful. But it really gets interesting only when you do multivariate analysis using machine-learning algorithms.

Now, this was interesting. So with that many data points, I have no way of really tracking them, but when we fed a set of features -- in this case, it was slope balance, the slope of the balance curve, the slope of the cadence curve, the average rotation, the slope of the minutes, the extent of activation and session heart rates, it turned out that the algorithm could predict, and patients had not seen before, how they would cluster in terms of the patient-reported outcome scores.

And then when we had some datasets that were actually not raw data, they were compiled datasets from the algorithms within the sensors. So this is a sensor that actually looked at -- took the heart rate and the sed count and some other data points and created some measure of metabolic output. It was extremely accurate. The R-squared value was 0.7, which is remarkable in predicting clinical outcomes.

Now, these are consumer-grade wearables used in context, and no one data point, except for this one, was that useful if you used machine learning, but it's pretty remarkable what we can do with them, which was something that you couldn't do before.

Now, when we talk about the devices and sensors put in the hands of surgeons, you

have to not forget that this has to be contextualized because this is not the only thing that's moving forward. So what happens if you add SMART technology to robotics, to 3D printing, to AI, to sensors, to avatars? I'm going to show you a couple of those suggestions.

I love this video. So what I will show you in just one second is what happens if you take a SMART device, put a computation platform, natural language processing tied to an AI machine, a great avatar, and sentiment analysis, which is the ability of the software to listen to you and figure out what your intent is, whether you're angry, what your mood is.

Now, what you're going to hear is not scripted; it is literally the machine listening and speaking to somebody, and then think about that in the context what if that machine had access to your medical record and say, in the back end, the cloud, something like the IBM Watson entered to help you with diagnostics? So you can play it now.

MACHINE: "Hi there, Angela."

ANGELA: "Say hello to the audience here at MobileView."

MACHINE: "Hi, audience. How are you?"

ANGELA: "Is this the biggest screen you've ever been on?"

MACHINE: "I think so. Everyone looks like ants from here."

ANGELA: "Don't squash us."

MACHINE: "Okay. I'll try not to."

ANGELA: "What is the future of artificial intelligence?"

MACHINE: "You're talking to her."

ANGELA: "Thank you."

MACHINE: "Don't mention it."

ANGELA: "Bye."

MACHINE: "Wow, that was quick visit."

DR. BINI: That last one got me. That was a quick visit. That's clever, it's sassy, it's

funny, but you start thinking about now -- you'd go to her if she had all the right answers pretty much every time. This is starting to get to the point that it's no longer a little sci-fi game, right?

This is a company from Silicon Valley that thinks that sometime in the future, if you've got a big chunk missing out of your tibia, they'll just put a print on it, print the whole thing. There's vessels, blood vessels, muscles. Okay, it's not sci-fi anymore. We're printing organs already, where cellular printers, bioprinters are out there. It's just literally a matter of time figuring out the physiology.

So at this point, unresolved SMART questions are how much data, what kind of data, what standards for reporting, what normative values? Are we ready to move away from causality into associative data analysis? Liability questions have to be answered. Who has access to the data? Who owns it?

At the end of the day, what we want is this: This is a car. Most cars today have 50 sensors on them; there are about three microprocessors, but this is all you see. The rest is either automatically managed elsewhere or you have access to it through different modules, but we need a dashboard that synthesizes all of this information and makes it useful to us.

And when you go back to this thing, realize that when those boats go to 55 miles an hour, it's because they're both hydroplaning on both foils. They didn't know the ship could do that; they thought it was impossible 1 month prior to the event when they, by mistake, foiled and had to figure out how to control the boat at that speed.

So as we introduce new technologies, there will be unknowns. It will be challenging for us to have standards around unknowns, but we have to be open to that possibility and then use those opportunities as they come up.

Thank you.

(Applause.)

DR. YATES: Our next speaker is Dr. Mark Froimson. He is the immediate past president of the American Association of Hip and Knee Surgeons and yet another dear friend. Despite the fact that he is from Cleveland and I'm from Pittsburgh, we've put our city rivalries aside. Mark has over 25 years of experience as an orthopedic surgeon specializing in hip and knee replacement surgery. He has had significant health system executive leadership roles, including serving as a hospital CEO within the Cleveland Clinic system and as chief clinical officer for Trinity Health. He's an innovator and early adopter of APMs, including bundled payments.

Dr. Froimson.

DR. FROIMSON: Great. Thanks. And it's a pleasure to be here, and congratulations to everybody. I always hate following Stefano because he's got all these great videos. And he always talks about the future. I'm going to talk a little bit about the past to kind of put this a little bit philosophically and contextually into -- you know, the question was utility of SMART technology in clinical studies, so I want to talk to you about sort of where we are, where we've been, and why that's not really satisfactory.

These are my disclosures; they're not really relevant for this.

You know, when we talk about technology adoption, I love this little cartoon because most of the time we're the little kid that's chipping away at the wheel, and we all start there, and then at some point we're the kid who's got the strap and thought that was the greatest innovation at one time. So I think we always have to see ourselves on this continuum.

When we talk about new technology, it's important to ask practical questions. So what is the clinical or business problem we're trying to solve? Who's going to benefit? Importantly, in health systems, who's going to pay for it? How is it better? Is it incremental

or a true leap? And then are there negative and unintended consequences? And then there's a whole slew of additional questions about how it should be introduced. And should it be a pilot program or a scaled solution? I mean, we're always talking about various things that we can introduce. By the time we pilot them, often they've already gone out of date, and it's unclear what to do with that data. Are they point or comprehensive offerings? Do we use existing tools and systems or new offerings? So a lot of things like that.

I was asked so what effect will this new technology have on clinical study design and outcome measures and doctor visits, and what role should professional societies play in validating these new measures, and I think these are fairly complex questions. I think what we know is that there will be a significant impact of this technology that's going to depend on our ingenuity, imagination, and the amount we're willing to invest. We know -- and I'm glad we're going to hear from patients -- that if we listen to our patients to design our clinical studies, respond to what they want us to answer, contributing to the care of future patients will be more successful. But the findings are always going to surprise us, and we have to be ready for some unanticipated impacts.

So I like this comparison. This was the papal inauguration in 2005, and it's a religious experience for people who go; they want to experience it directly. In the intervening years, the iPhone was introduced, and who would've thought that all those people having that pilgrimage would now experience it through the screen of their iPhone. It's a really remarkable statement on how technology can have impacts that we really did not anticipate.

So we do clinical studies. Why? To advance our knowledge about natural history of disease, correlations and causation, interventions that we might want to offer, safety of these interventions, the comparative effectiveness and the cost effectiveness of these interventions.

And this report comes out from the Association of Scientific, Medical and Technical Publishers and it's startling, 2.5 million articles produced a year in 26,000 journals. So we're doing a lot of writing and publishing. We've all heard of publish or perish, but what was remarkable to me is that about 50% are read only by the author or the reviewer. You know, we ought to ask ourselves how productive are we really being in that.

And so let's talk about clinical studies. They're expensive. Informed consent can be problematic. We need large numbers. There are lots of variables to control for. I think you heard some of that, where we try to control for a single variable, but there are so many other things going on at once in these complex systems. And then there's this notion of statistical significance that we can often achieve, and we often wonder whether that difference is clinically important. And so sometimes we have underpowered studies, and the relevance for our practice is uncertain.

So you know the types of clinical studies. I want to talk about these just very briefly and some of the concerns that we've had about them.

The randomized controlled trial is the gold standard; there's no question about it, but it's very expensive, and I would argue that it's probably underperformed, and I'm going to show you an example of that. We don't know what the impact of randomization is. We know that informed consent is difficult. Patients fear a loss of control, and so as we're entering into this notion of a patient-centered world, doing randomized controlled trials is often very problematic for patients.

And there is this placebo effect. One of my favorite examples in arthroscopic surgery, for arthritis of the knee in which they compared the role of sham surgery with arthroscopic surgery and found that there was no clinically meaningful difference at a certain stage of osteoarthritis. What was the most remarkable aspect of that finding was that the sham operation patients did remarkably well. It wasn't that neither worked; it was

that both worked. And so we have to ask ourselves if we fully understand the impact of clinical trials.

Here's an orthopedic example of randomized controlled trials: VTE prophylaxis. Blood clots after joint replacement was thought to be a very clinically meaningful problem, and so probably no other topic has been studied with as much rigor as VTE prophylaxis after major joint replacement. Millions, hundreds of millions of dollars. You know, these studies have come before the FDA. And after all of this, decades and decades of work, no consensus has emerged about the superiority of any treatment, and in fact, most surgeons have abandoned all of those expensive pharmaceuticals and are using aspirin today.

And why is that the case? It's because there are some challenges with these types of clinical studies. The question is whether the cohort is relevant and whether the inclusion and exclusion criteria of randomized trials makes those trials less applicable to the patient who's in front of me. There's this concept of the tyranny of averages, and this is an interesting book if you're -- this notion that we're always trying to design for the average, but the patients who come to us require some precision. And when we look at those VTE studies, the lack of clinical relevance has to do with the fact that all the patients who were bleeders or clotters were removed from the trials, and so, therefore, those trials turned out to be fairly irrelevant because of all of the inclusion and exclusion criteria that are demanded by randomized controlled trials.

There's now a movement to look at studies that are based on claims data, and we know that there's massive amounts of data available in the claims libraries, the PearlDiver, the CMS database. Unfortunately, these are based on coding and not meant as clinical systems, and I like to call this the allegory of the cave. If you're familiar with Plato's allegory of the cave, the folks in the cave were just looking at shadows on the wall, and this claims data is really the shadow, the mirror effect of clinical events. It's not true clinical events,

and we have to be careful about extrapolating data.

I flew in this morning on a Southwest plane. You know, it's a tragic event, and when you think about it, one person died -- it was a very tragic event, one person died, and it then called for the inspection of all of the same types of engines and fan blades. We know where every part is. We know what should be done. The question was should it have been done sooner? But how many people are dying in medicine with issues that we should be tracking and we don't, and that's, I think, an important point.

So that leads us to registries, and these are large datasets. The problem with registries is that it's voluntary participation, and the question is should it be mandatory? And it's been really challenging to get organizations to participate and largely, I can tell you, in our organization, due to HIPAA concerns, business associate agreements, data structural issues, and it raises the question that you've heard today about HIPAA and privacy issues. It's probably time for us to reevaluate this legislation and try to understand what are we thinking about with healthcare data when all of this data is proliferating around us and patients have been free to share their data on all sorts of things with all sorts of people, and the presumption is that we need to keep their data private, which I think is probably true, but we need to rethink about it because it creates some challenges.

Now I want to take us back. The physician-patient relationship is the essence in medicine, and the technology that we're talking about here today is an extension of the reach of the clinical team, and we need to use this technology to do what we do as physicians, which is to engage patients and to empower patients and families and to ensure that information is bidirectional, that we get patient data, we provide clinical instructions, care protocols, and reinforcing information that is patient-centric.

Just briefly, as I was thinking about this, what strikes me is that there are different types of data, and I'm going to give you three different ways to kind of look at that.

First is data we're collecting by other means that maybe we can use new technology to collect differently. There's data that we know we'd like to collect, but we don't have a reliable method. There's data that we can't currently collect but we know exists out there, so like the pH data in an infected knee. And then data about events and interventions that we're creating through this new technology that hasn't currently existed.

This is another data structure as we think about all of the different aspects of data that I think you heard about, so I won't belabor that. There are lots of forms of data out there that we need to bring together.

And then there's this, our attitude towards data, like data that confirms our own biases and beliefs. And I think that's pretty common. We can always find data that supports our own viewpoint, both in medicine and politics; data that raises new questions, so we would should be out there probing for new types of data, data that provides new insights, like is this bone about to fracture, something meaningful or data that compels action, like there's an infection.

And then there's this concern I have about data that's true but not useful. So I like the example of like how many dimples are there on a golf ball? Like, you know, in case you want to know, it's 336. But is that data that you really need to know? Is that really informative? And the question with all of these sensors out there is how much data are we accumulating that we just really don't need to know?

It wouldn't be appropriate if I didn't talk a little bit about value and the safe, effective, and efficient care at the right cost. So we need to be collecting that sort of data. You've heard a little bit about case report outcome measures. The key point I want to make with this is that as we were working with CMS on some of the mandatory bundled payment programs, we had to go to these top few buttons, which were simplified data measures to reduce the burden on patients. So wouldn't it be nice if we could automate that somehow

and change the way we're collecting data?

Think about clinical outcomes. We ought to think about different time frames, patient experience within the first 30 days, safety, adverse events the first 90 days, functional recovery within the first year, but survivorship and durability is going to be out for decades, so we need to be aware of that.

I think somebody mentioned this: choosing targets for a clinical study, an unsolved or poorly solved problem, something that has enough impact with either frequency, severity, or cost to the individual or society that's meaningful, where existing methods are not optimal. And perhaps we can use SMART tools to help us identify, using surveillance of large datasets, which problems need study, who among us is best able to study it rather than have everybody out there trying to study it who may have insufficient experience, what benefit it will accrue, and how long will it take.

I think that new technology can, as you've heard -- so I won't belabor this -- engage patients in clinical study, making participation easier, making informed consent patient-centric, reduced burden of participation in trials, so reduce the number of clinical visits. We can collect this data more remotely, collect it automatically, and actually improve our patients' compliance with our care protocols so we have more patients within the study for whom the data is valid. There's significant data that we can improve adherence to therapy, providing tools that look for medication compliance, SMART medication packs that identify each pill as it's removed, and then you've heard about telemonitoring during clinical trials to reduce complications. So these things are effective, and I think they will play a role for us.

I think it's important, getting back to registries, for us to start to think about every patient should be a study patient, and this notion that we have millions of joint replacements going in and yet a very small subset where we're collecting data, I think, is

really a disservice to the future patients that come along. Every patient should contribute; there should be democratization of study participation and ease of onboarding education and a consent process, better collection of existing data, and our ability to collect information not previously available.

So I talked a little bit about this, so back to the question that was posed. So what effect will this technology have? I think it will help us ensure patient engagement and ease the burden of clinical studies. I think we will change what we measure, and you've heard a lot about that from some of the other speakers. I think we can do this through virtual visits and continuous monitoring at different time points, so that should make it easier.

And then the question is will it give us new methods to better answer our questions than older imaging modalities? And we talked a little bit earlier about fracture strain, for example, rather than lagging x-ray findings.

And, finally, as a professional society, I can tell you that the clinical practice is way behind what we're talking about here today, way behind, and the question that we have to grapple with is how do we get your rank-and-file physician out in the world, who is significantly burdened by a lot of things going on, to adopt this, and how do we strike the right balance between offering new modalities and mandating that they utilize those new modalities? And we're having significant conversations today about standards of professionalism with regard to process compliance and outcome measure documentation, and I think that's really going to be a critical aspect in getting this into the mainstream and out from, you know, specialty centers where we're learning about this.

So, with that, thank you for the opportunity to be here.

(Applause.)

DR. YATES: Thanks, Mark.

Our next speaker is Dr. Rickard Brånemark, and he doesn't know it, but he's a friend

of a friend who is my partner, Dr. McGough, and also involved with osteointegration. He's currently residing at the University of California, San Francisco, visiting the United States. Rickard has been working in research, clinics, and business development related to the field of percutaneous osseointegrated amputation prostheses for more than 25 years. He is currently involved in several IDE studies using implanted electrodes.

Dr. Brånemark.

DR. BRÅNEMARK: Thank you very much. So, yeah, I will try to talk a bit different. So this would be about sort of more of that specific long-term project and where it might lead up to in the future.

And just to start with my fairly relevant conflict of interest. So since I've been running a company related to getting medical devices approved in the U.S., I have been seeing FDA as an enemy for many years, which was actually true in the beginning, I would say, and maybe I will come back and comment and make some more nice comments later.

So, anyway, this field of osseointegration and attachment of devices to the bone is actually based on the work initially from studies of microcirculation in bone tissue. So even though I think that we should focus on problems when we do research, sometimes research can go in directions that we didn't realize from the beginning.

So my father used an experimental device and then used a titanium material and anchor that implant into bone tissue, and he couldn't remove it when he was planning to do another animal experiment. And that was actually the foundation of modern dental implants, and my father did the first surgery in Gothenburg in 1965. And that moved on to percutaneous implants in the cranium exterior facial area in the '70s as well as some stupid SMART implants. So by the rigid connection to the skeleton, some engineers came up with the idea why don't we route vibration through the skull bone directly to the inner ear so it's like a type of cochlear implant, you can say.

So most of the work I've been doing has been related to amputees. The traditional way of fitting an amputee would be with a socket prosthesis -- that is a great innovation in itself -- but there are some limitations mostly related to the way that load transfer would transfer from the skeleton through the soft tissues to the external sock prosthesis, leading to pain and skin sores and a lot of discomfort.

So in 1990 the first patient in the world was treated with osseointegrated amputation prostheses, or actually not, because it was the patient that drove the development of the device by her needs. So she pushed hard to be having something that would bring her out of a wheelchair after a very bad tram accident where she lost both legs. This was before the medical device directive was implemented in Europe, and I would say that today we couldn't have started a program like this in this way, so that is something we might be able to talk about later.

So, finally, after many years of struggle with my enemies at the FDA, we got the HDE approval, and we are now close friends. No, it's actually something we can come back to again. It's amazing how FDA has changed in the way they interact with companies. I think it's utterly good.

So instead of a socket, we have to have something that is penetrating the skin. So this is an illustration of what just a stupid implant can do if you just make sure that it can interact with a body. The body is a fantastic machine, and the control system that lies in the brain is so remarkable. So we should more think about interacting with the human body than just measuring how can we interact in the best possible way.

And it's also so that even if we can do fantastic things with attachment, etc., so what is it that we really attach? So how good is a prosthesis like this? And that leads to this product that we've been running now originally in Sweden and now is in the U.S. for many years. So not only attaching in a good way so you can use the normal brain control system,

but how can we drive these prostheses in a more natural way? How can we pick up brain activities, and how do signals originating from the brain go out through the body and control the way the device is working?

So one thing is to control. We've already addressed the issue of bidirectional. We also need to sense a hand. Without sensor function, you can -- you should amputate it; it's not useful. So we developed an upgrade to the existing implant system where we can route wires through the system out through the cortical bone and place different kind of sensors, etc., on muscles or nerves.

What does this do in its first generation? So this is a patient with implanted electrodes, but here we first used external electrodes that are picking up the muscle potential via the skin. And you see that there is a very poor comparability, because when he's moving the arm, the muscles and the sensors will be misplaced, and since he's far away from the source of the signal, there will be crosstalk. So we cannot really have a stable attachment. So, instead, now we're shifting to his implanted electrodes that are placed directly on the muscle, and he can regain full range of motion and perfect control.

So what did this really mean for the patient? Why, you know, fantastic, you can show some nice videos and so on, but this patient moved from having just an osseointegrated device to a device with more control, and he said, okay, that's really changed my life. It's not really a prosthesis anymore, it's a part of my body, and I'm never taking it off anymore. He's using his arm 24/7, and that's just with this added motor control.

So we also added sensor feedback, and this is in its early phase, and let me just show you one short video here. So we have some nerve caps around one of the nerves, and in a prosthesis there is a pressure sensor in the fingers and where then we have a new stimulator that will stimulate the nerve so they get some kind of electrical feedback to the

nerve so he can control the pressure of the grip.

But, of course, we would like to drive this into the future, and this is just a picture I borrowed from MIT; it's a new advanced combined ankle/knee joint system with a lot of sensors for feedback and for control. So how can we really add natural motor control, and what about proprioception that will be needed to really drive an external limb in a natural way?

Can we use this system to upgrade it with the added technologies with SMART sensors, with stimulators, etc.? Well, one way of doing that is not just to use sensors actually to rebuild human parts; there are ways that we can take small pieces of muscles, we can reinnervate, we can revascularize them, bring them together as agonist/antagonist pairs, just like the biceps and the triceps, bring that into an amputated limb, and then instrument it and drive a future sophisticated prosthesis.

And this is exactly what we now have IDE approval to do, to use a combination of a bone anchor device with wired solutions, build small biological constructs, instrument them, and be able to get maybe natural proprioception and all the mechanisms we can have today. And this is just in its infancy.

So what can we do? Yeah, we can bring together the different disciplines, and here we have, for instance, top middle, Dr. Jonathan Forsberg, he's the head of Department of Defense osseointegration program. We have the LUKE Arm, the most sophisticated arm prosthesis available, approved by FDA. We have the MIT labs here illustrated by Hugh Herr. And then we have Todd Kuiken from Northwestern, the leader when it comes to upper extremity, and also the innovator of the TMR surgery that will be represented here by a patient shortly. We have the implant system, we have actually Dr. Lutzer, maybe an old picture or maybe he looks exactly the same, representing biomechanics, that will be utterly important, and we can use also this to instrument and learn about biomechanics, and this is

a nice research platform.

And to all of this, I would add that now we see that if we can collaborate with the regulatory authorities in Europe and in the U.S. and build standards and systems and understanding together, we'll be able to drive this much faster. So it took us about 25 years to get FDA approval for the stupid system, and it took us just a few years to get IDE approval to start to look into SMART implants. I think that's a fantastic improvement. Now I'm happy to be here again.

So, with this, I would stop here, but I will also now introduce the Fireside Chat, and I don't know if we should arrange something. So the plan here is that we have two patients. I will represent the Walter Reed Medical Army Hospital because they are not able to be here. I know that some people are but not the surgeons. And I've also been involved in the treatment of a service member with amputation, and Dr. Bini will illustrate his case. So the plan is that we should try to get some kind of informal seating here in front, and we should just introduce the patients, and then the floor will be open for discussion. So let's have a reseating.

DR. BINI: Mr. Piccolo, if you could come to the front. Mr. Piccolo is very thoughtful. He drove a couple hours to the airport and then flew all the way here to be with us today. He is now -- how far away are you from your knee replacement?

MR. PICCOLO: Oh, I had that August 10th of 2017.

DR. BINI: And are we going to be all four of us up here? Do you want to come up, or do one at a time?

DR. BRÅNEMARK: Yes. So this is my driver this morning, Mr. Cicero. We were trying to take a shortcut, and we almost made it. So I will actually leave the word directly to you. So give us a very brief summary of the treatment that you are underway with.

MR. CICERO: After my injuries in 2010 and proceeding to get back to normal, my

first part of this journey was to be involved with TMR, which Dr. Brånemark just explained, and I'm kind of picking it up from the back end, but they took my bicep and tricep, and they split them in half, and it gave me the ability to now have the nerves from my hand that would tell them to open and close that will actually work in conjunction, and unfortunately, you're seeing some of the technological issues that go on with this hand, with this arm system. And what I am doing, though, is when I genuinely think to open and close it, it closes and then it opens back up. Also, I still have to maintain control of the bicep and the tricep as well. But the magical part is this doesn't exist in my arm, but I've tricked my brain into doing it, and we can talk more about that later.

Then came along osseointegration, which we started that in 2016. I was the first guy in the United States to have my arm completely done and integrated with it, and ever since then, it's been absolutely fantastic, and we've been working on my leg, and as of tomorrow, I'll be 7 months post-op, or 7 weeks rather post-op from Stage 2, and it feels fantastic, and I can't wait to get up and walk on it.

DR. BRÅNEMARK: Please stick to the protocol.

MR. CICERO: Say again?

(Laughter.)

DR. BRÅNEMARK: Stick to the protocol.

(Laughter.)

DR. BINI: So, Mr. Piccolo, can you tell us a little bit about where you were before your knee replacement in terms of your activities and your pain levels and then maybe tell us a little bit about your experience with your new knee?

MR. PICCOLO: I've been a cyclist for, I don't know, the last 30 years, a tri-athlete, a lot of mountain running, so over the course of those years, I don't think I was running correctly; my knees started bothering me. I was taking cortisone injections for a while, but

you know, that doesn't last. You know, sometimes it lasts 2 months, sometimes it will last 1 day, so that was no -- there was no end there to that. I finally was getting really tired of it, and I couldn't run anymore, my cycling was dropping way down in the way of mileage and days on the bike, so then I just decided I wanted to have a knee replacement, and I contacted Dr. Bini's office at USCF and proceeded to go from there.

I had my surgery in August. At the time, they had asked me to wear these devices, and I didn't know what that was all about, but I had worn the Fitbit previously through my insurance company to "lower the premium," you know, so I did that for about 3 years, so I was used to wearing a Fitbit. I had worn a heart rate monitor for many years in my cycling and swimming just so I can keep track of myself.

But wearing the three devices from Dr. Bini's office, I wasn't really instructed to monitor all that except for the Fitbit, which I did regularly to keep myself honest on how many steps that I was taking a day. It worked out really well because I was used to wearing that, but the other two devices I didn't know what that information was. I was trying to look it up, I didn't understand it, and so actually I was just wearing it for his benefit more than mine at the time.

So at the end of the day, I wore that for 3 months; I wore it every day, day and night. I would charge it at night. One of the devices was really difficult to recharge, and at one point I like gave up on it for like a week, and then I decided to go back and try to recharge it, and it did start to recharge again. So then I wore that until the end.

After 3 months, it was sometime in November, I believe it was in mid-November, the program was over, but I continued to wear the Fitbit for maybe another month, but by then I was back on my bike, not real well, but at least I was up and moving around and on, you know -- and that Fitbit sort of helped me keep myself -- just kept myself honest with myself on how far was I walking. And once I was there, I just progressed. Now I don't wear the

Fitbit at all; I'm back on the bike. I don't run anymore, very little swimming. I'm not near the ocean, so I don't do my open water swim and I don't like pools, so I just cycle. That's all I do. I do a lot of walking, but mostly cycling.

And the surgery went well, no problems. My knee feels great, it's a little stiff, but that's better than the pain levels that I had before. The pain levels are intense when you have knee -- when you have knee and hip and ankle issues, but I feel great, and I'm happy about it, and I may have my left knee done here in the next year or two. We'll see how that goes; we'll see.

DR. BRÅNEMARK: So, Richard, you know you're already a guinea pig.

MR. CICERO: That's my name for myself, by the way.

DR. BRÅNEMARK: Yeah. So even though the leg device is FDA approved, the arm device is not, so that's an IDE study. And we are also discussing -- I know you've been discussing with your surgeon at Walter Reed that maybe it will be a part of another IDE study where that implant will be upgraded with the implanted electrodes. So can you say something about, you know, the risks for yourself, the benefits for you, and maybe benefits that go beyond yourself and how you're thinking about those?

MR. CICERO: Well, I can tell you, first off, the benefits far outweigh the risk. The pain impact of this, for me in particular, is little to none for both arm and the leg. The greatest change in my life is, post-TMR both on my arm and leg, to feel a hand that doesn't exist, to feel a forearm that doesn't exist, and to feel my lower extremities that don't exist, and I can't wait to have them actually connected and hardwired to the prosthesis because when I genuinely think open my hand, I'm thinking and it's registering in my brain that it's opening and likewise when I close it. When I go through the certain range of motions and certain tasks with my leg, I get the same kind of feedback in my leg.

So the end state of being genuinely hardwired to it is fantastic for me, and knowing

some of the things that are on the horizon for additional contacts to the brachial plexus and so forth, it's going to shoot the technology capabilities through the roof, and it takes somebody like me to step up and do it. You know, when you spend your life getting shot at and jumping out of airplanes and, you know, working with dogs that bite people and hunting bombs and things like that, this is easy and it really is. And people ask me all the time, aren't you scared? I'm like, really?

(Laughter.)

MR. CICERO: This is the easiest thing I've done in my life. And it truly is, so -- and I've got a vested interest. I've got two boys that are active duty and a nephew, and for every young man and woman that is out there serving our country, and they see me and they say, well, you know, if I get banged up, look at this guy, he's working on becoming the Bionic Man. Why not? Let's go forward and let's make things happen. And that's my part, to be able to continue to serve in my community, and that's what this is going to do and do even more of.

DR. BINI: Mr. Piccolo, I want you to go back a little bit to some of the points you made, which I thought were really good, about the use of sensors to monitor patients. We intentionally didn't tell you what to do with the sensors; partly, we didn't want to cloud your experience with them, also because we didn't really know what to look for until we got the data back. But some of the sensors are valuable to you, and there were some challenges. You were telling me about the number of -- charging them and maybe the number of USB ports you required and you chose to use one but not the other, so what was it about the devices that you thought were more compelling one way than the other? What about them would make you use them again, for example?

MR. PICCOLO: Well, the Fitbit is pretty simple to understand because you can read that on the screen on your wrist and you can also download all that information.

Information that was downloaded on the PAI and the SLICE device, I didn't know what it -- I didn't know, I didn't understand it. I wasn't trained on what to look for and understand any of that. The Fitbit, it just shows you steps, it shows you -- I think it might show some calories, I don't remember, but that's really basic easy stuff, you know, to understand. But all that other stuff, if it was -- if I was informed on what to look for, then I would get more into it. I like the technology part. I like knowing my fitness level at all times; I really enjoy doing that. And that was it, you know. I really did it for the study and so that other people can benefit from that as well, and seeing all the information today, I can see where all that can go and where it has already gone to.

So I'd be open to do it again at any other point for -- even today, if I was asked to start wearing those devices again, I'd put them on tomorrow. I'd charge them up, I'd put them back on, you know, and I would go back on it. I just wish there was more on the cycling part because a lot of this is just motion, running and walking. I believe swimming is now incorporated a little bit into that, but there's nothing really on cycling except I use a Strava, a running -- I mean, a cycling device on my phone, so that tracks my miles, calories, and -- you know, and how many feet of incline that you've done in a day. And that's beneficial to me, but I wish there was more information. I wear a heart rate monitor; I can check my heart rate at any time, but that's it.

DR. BINI: I think that one point I want to bring out is this -- it is going to be patient driven, that we integrate all these platforms one to the other, EMRs notwithstanding because they get in the way; sorry, but they are. But you want Strava hooked up to the sensor, hooked up to our database. So people have already solved the cycling question. Why can't we integrate them? And that idea, that concept that the patients are requesting us to integrate with their existing environments is going to be driving a lot of this innovation. We do not live in a vacuum.

Any questions from the audience for either of our members?

DR. BRÅNEMARK: Yeah, let me ask Richard another thing, and that is related to where we should go in the future because, you know, there's a lot of talk about patient-reported outcome measures and that sort, but we need to appreciate that we don't really know what we should measure.

So, for instance, there is a vast effort now -- there is the HAPTIX program driven by DARPA for artificial sensory feedback, and still nobody really knows if that is relevant for the patients. There are some investigations indicating that, but we don't know. And I think what we can see, also, with some of the stuff that we do that would be nice, research platforms for things that -- those that are running the programs initially didn't really realize.

But coming back to maybe you can -- so if you could have feeling back and what we know today about the feeling that we can restore, it's that it's not natural. It will be much more of a tingling phenomenon; that is one thing. Maybe you can also comment a little bit about the discussion we had in your car related to if a powered elbow is important or not.

MR. CICERO: Those are both very, very key things in my life, you know. My first real experience with the sensation came when I started wearing a training prosthesis, and I was standing in a conference last year, and a doctor that's now become a very good friend of mine, she snuck up behind me and she was just tapping on the very end of it. And I turned and I said, ma'am, were you just touching my arm, and she smiled; she goes you felt that? It's like, yeah, but it felt kind of weird, but not in a bad way. And it became kind of a show and tell of, well, I'm going to close my eyes and see if I can feel that and see what it takes.

Now I do a little parlor trick with some folks, and one fellow this morning, I said I'm going to close my eyes; tap the arm and I'll tell you exactly where -- or within an inch or two. And he taps the back of the hand, I said, oh, that's way too easy; that's distal end on the outside. And I do those kinds of things all the time. So, yes, you genuinely get feedback

already without even those sensor aspects, so I can only imagine what it's going to be like, and yes, I do little things where I'll touch carpet with this hand and then I'll touch it with this one, or I'll touch various parts with the arm because the hand is sticky, so sometimes it will give me different feedbacks, or I've got on the bottom here you can see there's a little pad on the tip of the index finger, that's actually for using a phone. So there's certain parts that I'm continually learning.

You know, when I first stood up on this training prosthesis after 7½ years of not feeling the ground, and I close my eyes and I can say my foot is on the ground, it may not be what you would conventionally say, but for the first time my brain said, yes, my foot is on the ground.

And learning what capabilities are going to come is even better because before this arm, I had been using what we call a hybrid arm, which doesn't have a powered elbow; it's a passive elbow you lock in and out of places and you move with a harness. And I found that I was able to do so many more things independently with this arm because it could move up and down while this arm was doing something completely different, that when I would go back to a hybrid elbow -- because I was burning these up, which is a technology gap between the brand new high-speed 2018 hand and high-speed 2018 control module and the 2003 to 2005 technology in the elbow.

It's something that the businesses, the different companies know about, something we're working on through DoD and DARPA to try to facilitate, to resolve that because genuinely the other thing is my 6-hour battery doesn't make it from 6:00 in the morning until 9:00 at night when I'm out teaching or doing other things. Plus, it's not very durable anyways. So I have graveyard killed two of these, the rest have been rebuilt, and that's only since August of last year. And that's the level of intensity and the amount of things I'm able to do that just -- imagine being able to take a prosthesis like that, pick up grape tomatoes,

slice them in half, and put them in a separate bowl. I also like to cook, one of those weird little dichotomies, and I did the entire quart of those with this hand. And that's exactly the type of things we're talking about.

UNIDENTIFIED SPEAKER: First of all, thank you for sharing your stories with us, very much appreciate it. I'm interested in the adaptations that your intact body made. First of all, during your phase of injury when you didn't have the implants, and how you've been changing your adaptations since your implants have changed basically your life.

MR. CICERO: You know, that is a constantly developing learning aspect for me. If you notice, part of why I'm wearing shorts is the back of my left leg is blown out, and they were able to salvage that, but I only have about 70% on a good day feeling in my leg, and believe it or not, that's the wobbly leg. So now this leg is going to be much, much more stable now. Since it's direct connect, there will be no more stepping out of the socket or anything like that. Plus, I get physical feedback on this leg. You'll also see that I wear a boot on this, and this isn't just some weirdo fashion statement. I do it because I'm a step away from needing an orthotic, and it helps to facilitate that, and I can only imagine how much more stable I'm going to be.

As far as my hands and arm movement goes, it is just amazing, I mean truly. I'm constantly learning something every day, and I task myself to find what I refer to as my OT task of the day, whether it's something in the garage, something out in the yard, something I'm doing at the hospital, or something I'm doing on the range when I'm out teaching because I travel the country and teach guys like me how to shoot again. Or it's the simple fact of being able to properly demonstrate a two-handed grip again for the first time in 7½ years and then get out there and employ it. Does that answer your question?

(Off microphone response.)

MR. CICERO: I was right-handed before; now I'm only-handed. And, you know,

that's another part is the feedback I get from this hand because I also lost a large portion of the feeling in my left hand as well. So having the feedback from this side really validates questions I might have, and one of the things they said to me during some testing is you really need to be able to do things without looking at them. And I said you don't understand; I can't feel it in my left hand unless I look at it. So if I pick something up, I need to see it to make sure it's actually in my hand.

DR. DMITRIEV: Gentlemen, thank you for sharing your stories; they're wonderful.

Mr. Cicero, thank you for your service to the country. The question I had was to do a little bit more with just data management.

And, Mr. Piccolo, you alluded to something that piqued my interest, and that is you wore a Fitbit before the operation to lower your premiums with the insurance company.

MR. PICCOLO: Well, that was years ago, okay; that wasn't anything to do with this situation now.

DR. DMITRIEV: And that is perfectly fine.

MR. PICCOLO: Okay.

DR. DMITRIEV: It gets to the crux of my question, and that is, is there any hesitation on either one of your parts in terms of what the data will be used for or who will get the access to whatever data, whether it's performance of your device or your healthcare status or just a general recovery from surgery, whether it's, you know, the insurance company or the Big Brother or whatever else it may be, once the data gets into sort of the cloud or the domain of ether where the internet resides right now?

MR. PICCOLO: I have no fear of that at all. I mean, that information was going to help the next person down the line. I'm sure it's going to be more beneficial for a person like Richard, you know. That information should be shared, and I haven't -- I have no qualms about that. My financial situation, yeah, I would definitely have situations on that,

you know, but no, the medical information should be shared. Again, I have no qualms about that, you know. It should be shared, you know. That's why we're all here; that's how we evolved over all these years. You know, I mean, jeez, it's like pasteurization of milk and just everything else, and if we didn't have that, where would we be today, you know? Where would we be without all this stuff for this gentleman right here, you know? Years ago it just didn't exist, so to me, it should be.

MR. CICERO: Well, likewise, I pride myself as having the ability to be an ambassador for what I do, so not only do I actively seek to gather more information, I pass it on back to the hospital as soon as I learn something new, and I'm out there constantly showing the other guys what's available and what things are going on. And, heck, I was in Louisville for something completely unrelated a couple of weeks ago and realized they had a big wheelchair basketball event going on and ran into a bunch of amputee veterans that were there and also a fellow who is a double AK from the San Francisco area, and I said, hey, and he saw what I was talking about. Well, the guy says, like, do you have any resource for civilians? I said, actually, let me get you connected with Dr. Brånemark and, you know, his whereabouts in California, and he was, oh, I'm in San Francisco. I was like, ha, I got the guy for you.

So, you know, that is exactly the main key and for -- the other thing is my community, we're all different. There's one guy with AK and a BK or just -- or double BKs or double AKs or missing both arms. A buddy of mine up in Maine, he's missing part of everything, and he lives a full life; he walks, he drives, he goes everywhere, and this is the technology that's going to grow and build, and someday we're going to go walk up to the back of a '76 Buick and pick it up because that's the standard I set.

(Laughter.)

MR. DURGAN: So Bob Durgan, Johnson & Johnson. First of all, let me join in

thanking both of you for sharing your stories, and Richard, thank you for your service and your sons' service to the country.

I'd like to go back to a point that was raised early in the day, which was, you know, whether or not we're collecting the data that matters to patients, so I'd just like to hear your perspectives on the data that's being collected in the clinical studies that you're in with what you would be interested in being studied.

MR. CICERO: Go ahead, you go first.

MR. PICCOLO: I don't know what that information was that was collected, you know. I mean, the Fitbit was easy, but the other two devices, Dr. Bini, I mean, what kind of information was collected off of there?

(Laughter.)

DR. BINI: Yeah, it's a -- question because I think on this one, I tried to loop that on the very last slide, I was running out of time, is that we don't know what data is collected. We don't know what data points are actually going to be valuable as predicted data points. So one of the things that we looked at, as I said, we had structured data and unstructured data, and we're trying to predict PROs, okay?

So here's what's interesting. A set of four or five features put into the algorithm could predict, say, the HOOS, but it was not predictive of VR-12. A different set of data points actually predicted VR-12, okay, and you look at those data -- those PROs and you realize that they're measuring different things. And we're still at that point where, for example, in the dataset that -- there was one device you collected, and I gave you no feedback, but it was probably the most sensitive, and it gave us data points every 2 seconds: pelvic tilt, pelvic rotation, things that we don't normally measure but we thought might be interesting, and sure enough, pelvic tilt was really predictive but rotation wasn't, but you wouldn't know that until you start doing these studies.

So I think at some point down the road we'll be able to get that data and then feed it back to the patient where that's usable. Right now, all we heard was, look, you got lots of data that wasn't usable to me. I didn't bother with it. But the one device that actually gave me a dataset that was useful because it was shown to me in a dashboard fashion that was useful, I used that. I used it beyond the time that I needed to because it gave me useful data.

So I think the answer to your question is still we're working on it. I don't think -- it's not quite a fair question in our construct. Now, it may be that -- I'll let you answer, Richard, for yourself because you may be getting datasets back that are far more evolved than the ones we're using.

MR. CICERO: Well, a lot of the data that we're getting is -- some of it's just downright instantaneous. You know, when you have the guy who's been in a wheelchair for 10 years and he gets up and he's walking and now he's out of the wheelchair every day, that's an instant home run; that is exactly the goal we're getting. We're also finding -- we're doing a lot of motion lab work where -- and some folks might not be familiar with this. It's where they put all the little dots on you and create the 3-D models. When you see yourself walking prior or doing something prior and then you see the anatomical changes -- and I'll give you a couple personal ones with myself.

My shoulders used to -- this one used to droop and roll in a little bit because that's how I had to control my prosthesis. Now I'm completely, perfectly square and symmetrical, both sides. The back pain that I was experiencing prior to OI, just from the way I walked, it is mitigated incredibly. We're learning things that we had never been able to do with a prosthesis before. One of them is the other reason I brought that Coke bottle, I can actually open a plastic bottle with my electric device without wearing it, number one; number two, I can put it back on; and number three, I can actually raise it up, drink from it, and do all

these other things that I'm finding every day that I can do.

These are things we can add to the database of skills that other guys are going to be able to learn, things they're going to be able to understand. I've got a good friend who's got one and got one of the very first surgeries, like my leg a couple of years ago, he's off doing Tough Mudders and doing all these other things that he never expected he was going to be able to do on a regular basis, and that is the instant concrete feedback, even though we're all at different levels of injury as we gather this. And the other nice thing is through the DoD, we're all sharing it and we all communicate well together, if not directly through the system.

Did I miss anything in there, sir?

DR. BRÅNEMARK: No, I think it's so that you should try to collect as much data points as you can. But sometimes it will be, you know, a fatigue for the study subjects to conduct too many questionnaires and too many hours and too frequent visits, so that is something we need to pay respect to.

And the other thing is that we need to have an ongoing communication with the regulatory authorities, but we always need to consider this. This is a business thing, so what about reimbursement, socioeconomics, employment, stuff like that? We need to consider that early, and we didn't do that when we started this in 1990, so we're learning the lesson, and I think that's something we should bring to the table for those that would like to come up with new devices. There are a lot of things to think about, and maybe, I think what's happening now at the FDA, you can take a more active role early to have -- okay, these are things you need to consider early on, because when it's later, then you're missing the possibility to collect clinical data points over long term, and that is what we need.

DR. BINI: So maybe we should tell them to go back to the university, and I can show

you some of our wearable sensors and collect the data passively; you can do it from home while you're just walking around.

So as I was saying, I was talking to Mr. Piccolo because I wanted to ask him, because he's a bit of a hero to me, it's like how many miles do you bike a day now?

MR. PICCOLO: Well, it's sort of dropped down from my normal -- I don't even know what normal is anymore, but right now I ride 3 days a week -- I try to do 4, maybe 5 -- and about 35 miles a day. But there's not much elevation in that; it's kind of flat.

(Applause.)

(Off microphone comment.)

MR. PICCOLO: I guess, you know, but that's my mileage right now. I try to do it, like I said, like -- I try to do it at least 3, I would prefer 5, but I've got work to do around my property, so I'm kind of busy, you know, remodeling and things like that, so that's it.

DR. BINI: So what I want to say is you don't pick that up with a HOOS, a KOOS, or a VR-12. So this is where the limits of our current methodologies to quantify and qualify the success of our procedures, or success of amputees, is that it's really limited by these very artificial measuring systems, and one of the hopes for our lab is to try to help create new datasets to help measure the difference in someone who can bike 35 miles a day, basically every day of the week, 6 months after his knee replacement versus someone who maybe isn't doing that and then why.

DR. DMITRIEV: Thank you, gentlemen. Thank you.

(Applause.)

DR. WEBER: Can we get the panelists to come up and have a seat and we can take questions for the panel?

(Pause.)

DR. YATES: We're running a little late, so we're going to start lunch at 1:15. That will

be the break time, just so the -- a little housekeeping here. We do have somebody at the microphone, if you want to ask a question.

MR. FIELDS: Sure.

DR. YATES: Is it working?

MR. FIELDS: Yes.

DR. YATES: Thanks.

MR. FIELDS: My name is Andrew Fields. I'm from Medtronic. I want to hear the panel's thoughts on the relationship between sensor-generated data and patient-reported data. Can current measurement tools like the VR-12 or the SF-36 be replaced by derivations of sensor measurements?

DR. BINI: So should I take that? At least here's my perspective after the study, which small as it was, we learned a ton. First of all, the metrics we get from sensor data are very specific to a specific task, so they step-count how far you've gone height-wise, metabolic issues. The patient-reported outcomes, as flawed as they are -- because they're flawed, they have ceiling effects, they have basement effects, they're limited in what they can measure -- do give you a sense of the patient's perception of an outcome. And Mark will have something to say about this as well, I suspect. But it is true that we need both. You can take a patient who's walking extremely well and is rather unhappy with their outcome and someone who's not walking well at all and is actually very pleased. And so to get the whole picture, you're always going to need both.

What we're trying to figure out is given that PROs are hard to get and the patients are loathe to get them, especially a year out, can we use some sensor data to predict an outcome, and then can you use the same data to change the course of the result? In other words, if can you pick up early that a patient's not doing well, can they be given more physical therapy? Is there a problem, are they infected, or something like that? Can you

pick up information early on that I -- to then act upon it and influence the outcome?

One of the things that we learned from our device is that it doesn't necessarily have to come from the physician. So what happened was, as patients are using their Fitbit, which is the one device that gave them feedback in our particular lineup of sensors, they're using that device to motivate them to do more, which they wouldn't otherwise have done. So now that gave us the opportunity to take these devices and feedback information in a way that actually changes the thing you're measuring, right?

DR. FROIMSON: Yeah, the only thing I'd add to that is I don't think it's an either/or, that you want to collect either PROs or sensor-related data. We're trying to collect as much data as we can because I think at this point we just don't really know enough about what to do with all of that data and how it correlates with an outcome and what patients want.

The other aspect is I think that we do want to engage patients actively because, you know, we're doing things for them, and we'd like to be able to hear from them. The real question about PROs is, you know, are we asking the right questions for those? I think, as Stefano said, you know, maybe they're not the right questions, but they are the validated measures that we currently have, and we need to look at their validation.

You know, in terms of the lack of compliance and the fact that it's hard to get patients to do it, I think we just have to look at that and ask a question, you know, to what degree do patients want to be engaged, because on the one hand we say they do and then on the other hand we can't get them to fill out the forms or give us the data. And so I think we need to study that a little bit more and understand what types of, you know, default criteria or motivations that we need to put in our systems, whether it's in the payment systems, in the, you know, policies, but somehow we need to go back to that notion that I tried to introduce, which is that every patient should be a study patient and that this data should be -- you know, if Medicare's paying for your joint replacement, perhaps you have an

obligation to society to allow us to collect that information so that we can, you know, learn from it.

DR. SAWYER: Thank you. I fully agree that we need both, and I think it's really important that we figure out how do we engage people in a qualitative but also in a quantitative way. And we've got lots of tools that we've got that are validated, etc. I think we need to move into more adaptive matching-type tools so we shorten the process, the survey tools.

But I think we also need to make sure that we're thinking about it from a behavior standpoint, a behavior science standpoint, in terms of getting some compliance with following through on the survey process and also the measurement side, and it goes back to that idea of the nuisance versus value ratio or vice versa. You want to make sure that you're giving someone something meaningful back, or they might do one or two surveys, but they won't stick with it, or they may not continue putting the measuring device on event after event.

So I think we have some homework to do in terms of how can we engage people with the right information so that we aren't continuing to add more questions on, but we do need quantitative and qualitative.

DR. BINI: The other thing I just want to add to this beautiful discussion, and then just listening reminded me of a few thoughts, that I always try to remind myself to not measure the potential future state based on the current state because there will be a time in the not too distant future where we will know an awful a lot about your comings and goings whether you like it or not. We'll know if you've gone to a refrigerator, we'll know you're coming out of the house, we'll know you've been in your car, we'll know how far you went in your new car, we'll know that you went to work. Your facial recognition software at the door, the front door, will know who you are and where you were. We may not need to

ask people for their data.

When I started at Kaiser Permanente a registry with a bunch of my colleagues at Kaiser back in 2002, we had to collect 90% of the data in that registry by hand from the surgeon in the operating room on a piece of paper. Fast forward to today, 90% of the data is collected automatically in the EMR, and we don't need the patient or the physician to input data. It's just a lot of these questions go away if you start considering how the rest of the technology is moving around us and where it's going, and that was sort of the point on my last two slides of my talk is that it's all contextual.

DR. FROIMSON: Yeah, I just want to emphasize, you know, and add to that that I think we shouldn't be having this conversation separate from the conversations we're having with CMS because, you know, payment policy is important here, and currently we have, you know, the sense that there's an entitlement in how we deliver healthcare, and we don't have to get into the politics of that debate. But what Stefano says, I think, is going to have significant implications which is if you allow us to collect your data passively and you waive some of your privacy considerations for the collective good, perhaps that should go into some policy implications in terms of your cost sharing for the care you get. And that is actually the implicit tradeoff that exists with Facebook and others that we're having a societal debate about, but we're not having that debate in healthcare right now.

DR. SAWYER: I just want to follow up on that because I think it's really great. I think it's really important that we also think about how do we contextualize that information and yield an actual insight, so whether it's quantitative or qualitative or the combination of both, we need to get at the actionable insight. And I've sort of nicknamed a phrase called matta-data instead of metadata, but it's the data that matters, and the people that we asked to participate in the studies, they really understand that, and that drives them to continue to engage in the questions and the process if we can show them why it's

meaningful and meaningful to them, not just to ourselves in research.

DR. YATES: I'm going to interject a question only because it follows up on what has just been said, and the question is, is obviously a lot of the patients that are involved with sensors and external sensor data collection, they're motivated, they're engaged, they volunteer to do this, you ask them to, and they say yes. But do we have any background information from psychology, psychiatry, from sociology of the distribution of the paranoia quotient that might be there that is separate from emotional quotient, intelligence quotient, that's separate from mental health problems?

I mean, there's got to be a distribution of people that have a sense of paranoia about their data being collected that ranges from I don't care, you can have whatever you want, to those people that sit in tinfoil hats and have escape rooms and keep in mind that the conspiracy in *Conspiracy Theory*, Mel Gibson was right.

So, anyway, do we have any background noise? And the reason I say that is, is if we start attaching some of this metadata to the basic healthcare needs of some of our patients, do we run the risk of marginalizing those patients that carry a heavy paranoia quotient, a heavy sense of not wanting people to be in their face? Do we run the risk of pushing people away from a total knee or from a total hip?

DR. FROIMSON: Yeah.

DR. YATES: So I throw that out to you because --

DR. FROIMSON: Yeah, I don't --

DR. YATES: -- I think it follows on --

DR. FROIMSON: I don't know --

DR. YATES: -- what you just said in terms of making a connection with CMS and everything else.

DR. FROIMSON: Yeah. I don't know the answer to that question from a behavioral

health or mental health standpoint and how you deal with the truly paranoid or those who are disengaged from the healthcare system, but I do think it raises the point that I was trying to make earlier, which is that we have to ask the question as to whether study patients are representative of the general population and I think that's the point that you're getting at, which is patients who are willing to undergo -- you know, to participate in studies have a unique set of characteristics that we just don't really fully understand and we haven't fully studied. And so often we do these studies, we get results, and then when we apply them to general populations, we find that the results are different, and that's why we have to collect data on larger sets of patients, and there is a role for registries even though we've not done them very well thus far.

DR. YATES: Well, then just one last question, and then I'm going to be quiet, but it's an important regulatory question. But, Dr. Sawyer, I mean, your slides with all the different technologies that are out there, I mean, I'm sitting here with a huge screen, and I thought I needed reading glasses to read it. It looks like the wild, wild west.

Are we sure that all of these studies, all of these different new technologies are all going through standard procedures for clinical trials, and are they registered clinical trials? I'm worried that with the new technology curve and the excitement over everything, that a lot of these, you know, aren't registered, and I mean registered in terms of a traditional trial registry. Are they going through that process in this industry or this new set of endeavors? Do you have a sense of everyone playing by those same sets of rules? And I say that because orthopedic surgeons will use the literature like a drunk uses a lamppost, more for support than illumination.

DR. SAWYER: Wow. Well, thank you. Thank you for those kind remarks on orthopedists.

(Laughter.)

DR. YATES: I represent those remarks.

DR. SAWYER: Well, what I will say is I think we need to actually map out some trial format, standardize the way that things are being evaluated, and we have a lot of very, very early research going on with these technologies, so I think it is right to say that we need to standardize the way we're doing testing instead of trials in a responsible way.

I think that one of the things we need to think about is I think our studies and our innovation should be really user -- use case driven rather than technology driven, and it was mentioned earlier today that are we building technology and then looking for a use for it, or are we solving, identifying problems and solving them and innovating towards a specific use or need? And I think that's a really important thing we should think about.

So making sure that we're solving real problems, and the other is that we are doing, in a standard standardized and scientific way, that we're answering questions in a responsible methodology that you actually referred to earlier in clinical trials.

DR. YATES: We have one there that was standing, but he sat down. You're next.

UNIDENTIFIED SPEAKER: A question, especially for Dr. Bini. The sensor technologies, the diagnostic sensitivity/specificity improves when we layer algorithms on top of it then interpret multiple factors together. I'm curious how you think about the regulation of those algorithms. What should we be doing? Is it based on area under the curve? And then also from a postmarketing surveillance standpoint, as we move to larger datasets of patients, multiple centers, what's the role for ongoing tweaking of the algorithms and regulatory review?

DR. BINI: You know, I don't think I've got a good answer for you. I'm going to be honest about it because I think that the -- I'm going to have to maybe ask some of our FDA colleagues that are here how they're thinking about it. I wouldn't consider that to be an expertise of mine. I can tell you that the worry about optimizing the algorithm is maybe

slightly mis-founded insofar as that by the very nature, most of these will be machine learning algorithms that will optimize themselves.

The feature selection at this point would still have to be, at this point, literally like last month when we did this was manual, but it's going to be automated and the device -- once you have 100,000 patients, not 25, you're going to be doing the automated data selection, feature selection for the algorithms.

The claim that the algorithm can make or the recommendation, which -- what you're referring to there under the curve or some people used R-squared values, what have you, which measures accuracy of the recommendation and where that threshold should be, we've accepted a heck of a lot lower than 0.7 in the past, and also, you have to now tie that into precision medicine, right?

So we have accepted very -- well, we've accepted the things that are good on average, and I think you were talking about this, a turning of the average, but the folks at the perimeter who maybe don't even have the enzyme necessary to metabolize that drug and still they're given it, this is true for hypertensives, so how can we use what we're going to be learning about precision medicine to then tailor that R-squared curve to be specifically high for that patient, even though that particular algorithm may not work for another?

But I think it's a little premature; we're not there yet. That is the future, and in the meantime the FDA -- maybe Anton, you can talk about this; you're at the microphone. It's a challenging process. I think that the -- I'll be more than happy around 0.7 for accuracy for devices.

DR. DMITRIEV: Anton Dmitriev from the FDA. If I could just add to that, that we will have a session in the afternoon that talks a little bit about digital health and what are the current -- actually, both the cybersecurity and the regulatory session will probably shed some light onto the question that you raised.

DR. SAWYER: I was just going to add a comment to that. I think we have to also look at how can we design some studies and de-risk in the process but learn from them so that we're looking ahead and looking first at observational analytics and being honest that we're not going to overstate the case from the results, and then move towards, as we go forward in longitudinal studies, looking at more towards prescriptive and predictive analytics. But I think it's really important, and we get excited oftentimes when we're studying new technologies, and sometimes we overstate, but we should always be starting with observational analytics.

DR. DMITRIEV: Thank you. Anton Dmitriev from the FDA again. Thank you very much for sharing your perspectives. The question I had was -- had to do with tipping the scales for the benefit-risk of these technologies. Obviously, there's a difference between breakthrough devices, just like what we saw with TMR and Mr. Cicero's presentation and sort of canonical orthopedics, which is our standard of care, total joint replacement fracture fixation. So I think maybe a lot of folks or some folks in the audience will have a similar thought going on through their mind and that it has to do with if it ain't broke, don't fix it.

So from the standpoint of my adding a sensor to a standardized device, we're always adding some component of risk. But yet, if we don't think about the benefit, the long-term benefit, and that is what I'm trying to get at is are there specific areas that could use additional sort of intrusion from predictive analytics that could actually preempt or maybe address some of the adverse events that may happen down the road that would actually tip the scales more into the benefit, maybe not the immediate term, but the longer-term benefit associated with these technologies in the sense that we may actually obviate some adverse events down the road if we catch them early. And what would be some of these clinical areas that could use more of these predictive analytics that are now not available?

And I think some of you have alluded to this fact in your presentations where you

come to a clinical manifestation of a particular -- of some concern too late, and at that point, either the device or the physiology of a patient is too far down the road, and it requires a major intervention. So could you speak to that sort of benefit-risk, immediate and even longer term, so we could think about it a little bit differently?

DR. FROIMSON: Yeah, I'll start. I mean, I think you're raising a really important point, which is -- so take total hip replacement, which is arguably one of the most successful procedures, and now you want to add sensors to the device, and is this for the benefit of this patient or is it for the benefit of future patients because we're using this patient as a research subject and we're going to instrument all of these patients to learn more about the future? So that's an ethical question about the obligation of the individual to benefit society when he or she won't get individual benefit. You know, then it's similar to a number-needed-to-treat analysis, which is like how many total hips do you have to put sensors on in order to pick up one early loosening that may or may not have any marginal impact on the outcome, right?

So I think that's important and, you know, we always talk about total joints. It's not because total joints are a big problem today. They're actually, as you saw from the patient, they're very successful. It's that, you know, it's the old Willie Sutton rule, right? That's where the money is, like that's where there's a lot of procedures, and so commercializing technology in total joints gets a lot of attention because it's high volume, high revenue, I think you saw the number, 29 billion dollars currently. So, you know, money drives innovation, and it drives interest. We have to back up and say is there a problem there that we're really trying to solve, or are we just doing what was suggested, which is, you know, finding an application for sensors in the hopes that we'll have a finding at some point? I think it's a valid question, and I don't know that we have the answer.

DR. BINI: So I would not agree entirely with that. I think total knee -- total hip

replacement, we're starting to see data that actually we're about 80% patient satisfaction rates. Ninety-five percent are in place pretty much for the lifetime of the patient, but they're not necessarily always happy with them. And total knee replacements, we know we're in the 20% range; it's been documented for a decade that we haven't quite solved the issue, so I think there are opportunities still within knee replacement.

So Mr. Piccolo, at 8 months, although he's cycling 35 miles in a day, still has some stiffness in his knee, and he brought that up, and that disappointed me a little bit; I wish that wasn't the case. But is there something I can glean from collecting data on him that may optimize that outcome? So I think we still got a ways to go where some data we are simply not collecting may help us.

DR. FROIMSON: So the premise there is that if we collect more data, it's going to give us information on and allow us to change that 20%.

DR. BINI: Correct, but I think that's --

DR. FROIMSON: And it may be --

DR. BINI: -- not unreasonable for known data.

DR. FROIMSON: It may be that there's a normative question here, not a descriptive question, which is who should we be doing total knees on, and how do we know which patients are going to be the happiest patients, right? And how to -- you know, should we be doing this in regard to patient selection rather than trying to ascertain early failure rates or substandard outcomes after the fact?

DR. BINI: Yeah, agree and -- but to Aenor's point, the first point, there's this idea that we -- the dataset currently being collected doesn't sit within a known quantification, there's no normative dataset.

DR. FROIMSON: Right.

DR. BINI: So it isn't -- you know, us, in the academic world, it's our job, I guess, we're

supposed to create those normative datasets against which to then target outcomes. But at the end of the day, right now, we're using datasets that are basically registries that collect patients -- yes, 100,000 patients at 1 year or 2 years or 5 years, it's very, very blind information, and that's pretty much all we have to go on.

MR. OWENS: Mike Owens from the FDA. Just real quick, I did notice that, I think, the microphones are set up in a way that when everybody has them turned on, it takes away from the volume.

But my question is just we talked about the kind of generational potential for this technology, maybe it being iterative in monitoring, going to diagnostic, going to active. What is your threshold for you, if somebody came in to your practice and wanted you to use a new technology, if it were monitoring versus going into diagnostic and active? Is the threshold at the level of evidence, if it's just something that's adjunctive, different in your eyes than if it's -- you're using it to replace or be a diagnostic? What level of evidence would you want to see for that device to implement into your practice going through the different iterations of the technology?

DR. FROIMSON: So you're talking about patients' requests for utilizing new monitoring technology?

MR. OWENS: Okay, so for an implant, say you have an implant that had a sensor on it. If, based on what you were using it for, say it was just a monitoring of strain versus a diagnostic of a nonunion versus active versus treating it, what level of evidence would you want to see from the company or in the literature before you are willing to implement that into your practice? Would the level of evidence that you needed for an adjunctive, just extra information in a treatment that you already know how to do from start to finish, would you accept a lower level of evidence than you would if it's something that's potentially going to replace a critical part of your treatment? How would you look at the

level of evidence and your willingness to implement that into your practice for a new device with a sensor on it?

DR. FROIMSON: Yeah, you know, my sense is that I'm looking for, you know, safety and then efficacy data and then cost effectiveness data, right? Those are kind of the three big categories that we're constantly looking at when there's a new treatment. And so you need to show me that it's as safe, so there's no risk, additional risk to the patient, and if there is additional risk to the patient, that it's outweighed by some sort of marginal gain and that you've demonstrated to me, so if it's a fracture healing or an implant survivorship, that there is a measurable change in the ability to detect fracture healing or the ability to have actionable insights into intervening. So the burden of proof is, is there a practical value to the patient that outweighs either the safety risk or the cost, the incremental cost?

DR. BINI: I could add to that, that if there's a predicate device, then the question becomes, okay, you're doing it quicker, faster, better, cheaper? If there's no predicate, does it assume any data that we never had before or it's really been impossible to get before? Then I would have a much lower threshold if I think it might be valuable.

After all the other discussions around safety, efficacy, and cost effectiveness outcomes -- first, I think you did a beautiful job explaining that, but this idea of there are often things that I mentioned in my talk, things that I would love to have real-time, quickly. Bioburden in the wound would be a good one. Otherwise, I would send a culture, wait a week for it to come back to the lab, and that kind of thing. So things that we know impact outcomes but we simply can't measure it now, that that would be a pretty low threshold so long as it doesn't have any potential negative side effects. Even if it doesn't work, I'm okay to take that chance.

But if there's an excellent study that works really well already, that don't solve a problem I don't have, right? So I think Dr. Ferrara mentioned that earlier, it's like -- it's

really the key piece of all this is are you solving a problem that I have, and what cost does that problem entail to my patient or to me that you're solving? And then that changes how I will approach that particular query. Does that make sense?

DR. FROIMSON: Yeah. I just want to add one thing which, again, is to separate out the opinions around this table and at this event and at academic centers from your busy clinical practice because there are a lot of things we'd like to know, like is there some, you know, bioburden in there somewhere? But I will tell you, when we talk to our members and we talk to your, you know, really good surgeons who are out there, they do not want information that they can't utilize, and they don't want the risk of having excess information burdening them for which they might be liable but for which they can't do anything. So I think we have to be careful about the distinction between, you know, well intended and, you know, cutting-edge academic people who are looking for new insights and extrapolating that to, you know, the majority of surgeons who are out in the community doing good work who -- for whom extra information is a burden, not a benefit.

DR. WEBER: We have time for one more question.

MR. BARRY: So Don Barry, Mitek Sports Medicine. Just to follow up on that. Let's just say, for example, that infections were 5%, just a number I pulled out from no place, and you have a test that had a confidence of 5% false positive, 0% false negative, so now you're talking about adding another 5% to people you might have to go in and do something with. So just as a general impression, you know, what kind of level of confidence does that give you to use such a device?

DR. FROIMSON: Yeah, I mean, in clinical practice, something that has a higher number of false positives than the incidence of disease is going to be problematic, so there you put them equal, and that means that half the people that you're going to intervene on didn't have the problem that you went to deal with, and so there's actually a harm that

you've created to those 5 for whom there was a false positive that you've created an intervention. So without doing a lot of thought on it, my sense is that's not going to get wide acceptance in clinical practice.

DR. YATES: As promised, we're going to draw to a close at a little bit past 1:15.

Andrew, when do you want to restart? 1:50 was the original goal; go back to that?

DR. BAUMANN: Yes, 1:50 was our original goal for the start of the Cybersecurity Consideration session. Let's shoot for 2 o'clock, give some folks some more time for lunch and coffee --

DR. YATES: Sold, 2 o'clock.

DR. BAUMANN: -- and see you all back in here at 2:00.

(Applause.)

(Whereupon, at 1:16 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:07 p.m.)

DR. RICCI: Hello, everybody. How's everyone doing this afternoon?

UNIDENTIFIED SPEAKER: Good.

DR. RICCI: All right. So we're going to begin the session on cybersecurity and looking at SMART devices and how we can make sure that these devices are secure as they're deployed and used.

So my name is Linda Ricci, and my co-moderator is Beau Woods, and you know, we're both from the FDA. Do you want to introduce --

DR. WOODS: Hi.

(Laughter.)

DR. RICCI: So I'm going to go ahead and introduce our first speaker. This is Salwa Rafee. She is from IBM Security. Ms. Rafee is a security business leader for the public sector in IBM and manages its global business for healthcare, life sciences, government, and education. She has over 20 years of progressive leadership roles in strategy planning, e-health innovations, security services and products, consulting in complex program management with a firm commitment to deliver excellence. So thank you.

MS. RAFEE: Thank you, Linda.

All right, good afternoon, everybody. This is a tough spot to be in right after lunch, so I hope everybody had their coffee. I'd like to thank the FDA for hosting this great event. I think the morning session was outstanding, truly phenomenal and quality presentations. You know, that was the heaven of biomedical engineering, to look at all of the innovations and see what we can accomplish here. So my job for this session is to bring you back to planet earth and really take a look at our healthcare organizations, of our industry, and what's been happening and maybe bring you back to the cloud.

So, you know, we -- from our experience on the ground here, we are looking into working with different clients, small and big. We noticed three cybersecurity mistakes that some average healthcare organizations would do. Some of you might be guessing what these mistakes are. The first one is historical underinvestment in healthcare, and we talk about the big H that includes providers, payers, and life sciences. You know, we don't spend much on IT, and of that, we don't spend much on cybersecurity solutions; average 3% of the IT budget on cybersecurity compared to 15 and 20% in other industries.

Also, we talk about compliance, we talk about security, and we talk about privacy, and we need to differentiate each topic here because they are different. Of course, aligned within the same overall strategy of cybersecurity, we have many vulnerabilities in our enterprises, you know, with of course, the EMRs, the medical devices. Especially IoT for life sciences, we have the whole vision of integrating with IT and OT technologies and IoT, many vulnerabilities that would make our industry very vulnerable to cyber attacks.

And also we don't have that many of skills for security. We have so many tools in a given organization, we have so many vendors working in the same organization, some of us do not have a cohesive strategy of what's happening here.

When we talk about regulatory concerns, we are addressing each one of those four domains: resilience, which is really the ability of any organization to withstand change, to withstand big cyber attack or a big change that might affect the business unit inside the organization. An example here of what happened with the NHS in the UK with the WannaCry cyber attack. They could not function for 2 or 3 days because of the ransomware; they were a ransomware victim, and that was really an existential business from their part. So resilience here would have to be measured according to the ability of the organization to keep on proceeding. Of course, cybersecurity and then the privacy of PHI and the sensitive data.

And lastly, but not least, the data quality. We talked about the data points and the integration and the quality of the medical data and how this all would be integrated in a patient-centric approach.

What I would like to talk about here is a shift, you know, passing an audit. Just being compliant does not mean that your organization is secure, and we need to move this, I think, mental vision of just an audit-based, compliance-based approach to a security and risk-based approach.

So the biker here on the left side could be compliant because he has his helmet, he has an okay-looking, I think, functioning bike, and he can pass through maybe a good audit here. Our friend on the right side, perhaps, is taking more secure measures of going to a secure, better, innovative, better bike and really a much better helmet for protection.

And when we look at compliance and regulations, you know, compliance is a starting position. It's not the end goal, being compliant. It's really a great driver for organizations to think about the risk approach, to think about the data strategy, data protection, and really go from the -- really part of the organizational vision of transformation, putting a risk agenda including cyber risk, defining the controls enhancement and mechanisms, and it's really an ongoing cyber risk and compliance management.

We want to shift to the right here, when it is a continuous and ongoing compliance and security eco-site, when we are going from the identified risk to measuring that against the controls and the cybersecurity and it keeps going. It's not a one-time checkpoint.

And, you know, our topic today, of course, is medical devices: wearables, implantables, and IoT. We have already entered the evolution of IoT, everybody, you know, wearing the wearables and the Bitfits [sic] and implantable devices. Many of these devices, as we know, they lack the security measures. You know, many of the IoT devices are manufactured in different countries other than the countries of deployment. We have very

low visibility about these devices, the manufacturing standards, if any, the encryption that they were following. And also, you know, the software that they are using for that, it has to be protected against malware injections. We have very little information about that, and the visibility and the number in any given network is just not a very clear picture.

Looking at the visibility and the controlled gap, you know, in the '90s compared to today, before that the organizations had complete control over what devices are attached to their network, and so we had little incidence of cyber attacks. Look at us today. Some organizations or the clients we're working with really do not have much knowledge or visibility about what is attached when sending or receiving information in their own network.

And with this proliferation of data, we're increasing the attack surfaces in an exponential way with the attack vectors as well. You know, just last year we had 8.4 billion things connected in 2017. We expect this number to double within the next 1 to 2 years. We have four billion users into the internet by 2020. This is increasing the attack vectors and really making us all vulnerable, you know, and it doesn't need any big hyper-scale of cyber attacks. We are facing very sophisticated bad actors that sometimes take from it -- sometimes they have the agenda and they have the collaboration with that. So we have been experiencing, what we see, the WannaCry, the Petya, the NotPetya, Bad Rabbit, if you remember that.

When it comes to life sciences and really the manufacturers of the medical devices, they are faced by other challenges, which is really the integration of OT, IT, and IoT. What's happening in the robotics in the manufacturing field assembly lines, how is that integrated into the automation part of the production lines, and how is that going in alignment with IT security measures? You know, most of the pharma companies and the medical devices would be looking and being compliant with the GxP regulations, but you know, there is a

conflict here with the patching. If you remember, also, in WannaCry, the medical devices were really the big victims here when it comes to our side of the ocean because they could not be attached -- patched with the operating system and, you know, it's the GxP mandate of being traceable sometimes prevents us from the patching procedure.

Some of you might be familiar with this curve, and we use it as a standard in cybersecurity. This is really what happens when a given organization gets hit by a cyber attack. We call it the BOOM. Before that, we have the phishing email, the credentials would be stolen and databases would be compromised with sensitive data, and then everything would be known from a perspective of the data and the social media until the FBI calls the CEO of the organization telling them that there is a breach here and we need to take an action. And this is really when the BOOM is defined, when it is public information.

After that, on the right side of this incident, then you find everybody's talking about it, stock price is starting to fall, press conferences, changes in the C suite of the clients, and this is really when the organizations start to suffer from financial problems and legal issues.

We want to be staying on the left side, being proactive from a security perspective, but if and when that happens, if we are victim of cyber attack, we need to know what incidence response that we can adopt. So, really, automation and orchestration of all of these parts across each layer of the organization would be key.

We talked about the implantable medical devices. Of course, you know, the cochlear implants with the defibrillators, the pacemakers, the insulin pumps, and you know, many instance with the counterfeiting of these medical devices, the spoofing that can happen. Medical devices can be impersonated, living there on the network, behaving like a medical device but really gathering information, and it's very, very hard to detect.

When we look at the research area and the robotic surgery and the nanomedicine, they are all operating on -- you know, every medical device is on the internet. These

devices are connected by wifi, Bluetooth, or mesh networks and thus very liable to any cyber attack.

And the likelihood and impact really varies if we have a curve between the risk and the device type, the operating system and the configuration; you see that the more we go to the right side of this curve, it's a high risk of the medical device. You know, from a configuration perspective, look at the -- if we have an iPad that is hardened and have a good quality of data management, you go further to the right, and the internet browsing is all full of possibilities and vulnerabilities with that.

Looking at the operating system type, you know, if we have a medical device with no OS, such as a bunch of executable files, very low risk until we get to the RTOS, real-time operating systems, such as perhaps robotics on assembly lines that would execute commands as they happen, and all the way to the Windows, which is very high vulnerability that needs to be patched and it has many high-risk points of penetration.

Also, the device type: You know, the blood glucose monitor, for example, is just a monitoring device. If it was hacked, yes, it would give us false readings, but it's not life threatening. We move all the way to the right with the ventilators, and this is regulating, as recall, the closed feedback; that is a life-threatening situation.

I don't know how many of you are surfing the dark web, any hackers or ethical hackers out there, but if -- oh, okay. So we have one here. If you go to the dark web, and I think many of the organizations have some ethical hackers -- actually, some of the life sciences companies have hackers that would go to the dark web to see if any of their products are being sold in this part. If we go surfing in the dark web, there is Tor, which is -- you know, it's like Internet Explorer or Firefox; it's really a browser that you can get to if you are certified in the dark web. This is where you can find software that you can buy, devices; you can get your passports done if you're an illegal person. You can also find some body

parts, body organs, and you know, it's completely anonymous. You have to be -- have the right, actually, credentials to surf that. And when you look at that, if you look at, you know, x-ray machines, you know, medical devices for -- to be counterfeited. Actually, they also have ransomware as a service, free of charge, so people can go and get some ransomware software, use it against organizations as a service.

There is a special search engine as well in the dark web called Shodan that really specializes in the IoT devices, a very sophisticated search engine. It has servers in each country, in many countries of the world, that looks into the vulnerabilities, looks at all the devices, SMART devices on the internet, you know, SMART web cameras, SMART TVs, refrigerators, of course, computers, medical devices, and try to see where the vulnerabilities are. You know, this is part of the very precision -- the analytics that we see from this search engine, you see the top countries that -- these are the countries that have those devices that can be vulnerable, and it provides statistics on that. It really uses the vulnerability, and the Heartbleed Bug, this is a popular one in the popular OpenSSL encryption algorithm, known vulnerability, and unless you are patching it, then this is a big penetration point. It looks also at top organizations that can be vulnerable to those attacks and provide all the way to do that.

So what we are trying to see here is to try to evangelize a culture of security, privacy, and compliance. You know, how we do that is really layered defense across each sector of the organization, from the platform, the infrastructure, networking, data application, mobility, and cloud. Each of these products or solutions need to be intelligent, need to be integrated. I think there was a reference this morning to our Watson augmented intelligence. I think the way to go for cybersecurity would be cognitive, would be automation and orchestration. And, of course, the three magic Cs with cognitive, cloud, and collaboration. You know, we cannot do it alone; we have to collaborate with the entire

ecosystem.

This is what's happening in the innovation cybersecurity. We are going to see the rise of augmented intelligence, not just artificial intelligence. It's really the machine and human learning mobilities, the microservices across each enterprise. Cloud, we're going to see the adoption of blockchain happening here and really going hand in hand with the IoT and making sure that our organizations stay secure and private for our patients.

Thank you so much for your time.

(Applause.)

DR. RICCI: Thank you very much. Our next speaker is Darren Lacey. Mr. Lacey has been serving as the Chief Information Security Officer and Director of IT Compliance for Johns Hopkins University and Johns Hopkins Medicine for the past 14 years. He has been working in the technology sector as a developer, attorney, consultant, and executive for 25 years. He was the first executive director at Johns Hopkins University Information Security Institute, which is a national security agency center of academic excellence in information assurance. Thank you.

MR. LACEY: Thank you. Thank you for having me. Basically, I wanted to basically, after those very exciting slides, make mine as dull as possible. So if I could have put gray on gray, I would have. But the idea -- I mean, I think that was a really great introduction. I mean, you basically got a full -- you pretty much got the full thing. So what I'm going to talk a little bit about, and I won't use all 14 minutes, but I'm going to talk a little bit about basically how at least essentially providers, you know, think about security, especially with respect to medical devices and the topics that we discussed this morning.

The first thing I wanted to basically mention is that when we think about medical devices broadly, we look at it from a couple of different perspectives, and the main one up front is procurement. That's where most of the action is nowadays, although that's

probably the least effective place to put security because basically after you've bought it, you don't know 3 years later whether it's -- you know, has the security in place. Then you have configuration, maintenance, and updates.

And then, finally, the one that actually trips everybody up is end of life. Many, many of the medical device problems that I've seen over the years in my organization and other organizations are from devices, systems that are being used for some very specific purpose, but they're really no longer under support from the manufacturer; they're really old. Maybe they're sold, but they don't even write malware for it anymore. But I found that, from a provider perspective, if you can solve the end of life problem, you've actually made a lot of progress.

Now, what's great about what we're talking about today is end of life is a weird topic, you know, for implantables and those types of things, although we heard a little bit about it earlier, that sometimes they break or sometimes if they basically aren't designed to last for as long as your insides are, and that might be something that we think about as we basically go -- as we try to apply these to implantable or SMART devices.

All right, so this slide I worked up just recently because I actually listened this morning to what people were saying, and I tried to get a better sense of where -- of (1) the level of expertise in here is pretty remarkable, but (2) what you were kind of interested in? And what I wanted to say is that as we go more into implantable devices, and we go more into the SMART types of systems, and they actually -- they come to the attention of the enterprise security group, but traditionally those haven't come to the attention of the enterprise security group because they've operated outside the realm of IT. Well, I think the FDA's guidance on this and, you know, best practices are indicating that at some point along the way, the 12 people in the country who can do information security, one of them needs to look at this on your behalf.

And so, basically, those devices are starting to roll across my desk more frequently or, you know, my colleagues' desks, and with these types of devices, it's really all about the up front, and that really makes me nervous because, like I said, it may look great now, but after a couple rounds of hackers going at it or just the sort of natural bit rot that takes place with any application or system, it's not clear what it will look like in a few years, but we have to do more on the up front.

What I'm trying to -- I mean, I'm trying to basically inculcate in Johns Hopkins is that when we have a device like this that's new, the idea is to conduct a risk assessment. It is not a security risk assessment really. In fact, I always try to downplay that part of it. I say most of the problems that you're going to have with medical devices isn't because a hacker is standing at the door basically sending, you know, hacker rays at you; it's probably because the device is just going to fail because things fail.

So the idea is to not treat security like it's -- especially with these types of devices which network differently than others, don't think of it as principally a security issue; think of it as -- and not even as a product defect issue. Just think of it as, you know, a Murphy's Law issue. What are the kinds of things that can go wrong with the device? And then we just add security on top, security just being the kinds of things that people who are malicious can cause the device to do badly. More just a subclass of the failure, of the failure proposition.

And I just try to basically walk them through a risk assessment. It's all common sense. I mean, risk assessments of this type, if they're too structured or there are too many checklists along the way, that's an excuse not to think. What I want is clinical leadership, executive leadership, the researchers involved and those types of things, to use their big brains, because their brains are much bigger than mine, use their big brains to basically, you know, tease out what the risks are likely to be. I try not to basically treat security as

fundamentally different than that. We, as security people, we say, yeah, those things can happen and there are -- if malicious activity is involved, how would that -- you know, would that scale be -- would that scale the problem higher or cause some other unforeseen problems?

All right, once having done that, then you basically think about, okay, how do we test these things, and this is like -- this is the part that I am really struggling with because we've implemented, you know, testing programs for iPhone apps and those types of things, but testing medical implantable or medical devices of any kind, but especially implantable or SMART-type devices, basically covers the entire waterfront of advanced security technology expertise, and that means that in most hospitals and most healthcare organizations, that's about twice as much expertise as what we actually have available to us.

So the tricky part on this is you have to be able to go deep into network protocols, deep into application security, especially because a lot of things use some form of web servers on the back end to gather data if they're basically doing the internet of things thing. You've got hardware, I mean, the hardware problems essentially. You know, are you going to basically recompile the operating system, recompile the micro-operating system? I mean, are you going to try to reverse-engineer it?

Most information security folks in most hospitals can maybe do one or two of these with some degree of facility, but not all of them. So this means there will have to be some kind of Good Housekeeping, you know, seal of approval for this, but I don't know what that's going to look like because of all the Good Housekeeping seals of approval, possibly IBM could do it, but other types of organizations are going to really struggle with coming up with appropriate testing protocols for these types of devices and then basically having results that anyone can understand.

Now, lots of folks are trying to get into this space, and that's great, but that's really

the -- that's the hard thing; that's what we're all responsible to do in my little part of the world, and I'm just saying that if you expect it to be done locally, your security staff must be much better than mine.

All right. So I mean, I didn't want to leave it all -- everybody bummed out, so I do want to say there are good things happening. One is that unlike previous years, unlike, you know, maybe when jQuery became a thing or those types of things where people -- and they started developing Ruby on Rails and PHB, they actually didn't think that much of security at the time, 10-12 years ago, people didn't -- or 15 years ago they didn't think much about security. Now, any time you develop a new framework, security is up front. I mean, you know, a conference like this, there's no way you would have people talking right after lunch about security; that just not would have happened 10, 12, or 15 years ago. The frameworks, the idea that they are at least talking about, if not doing security effectively, they're at least talking about it.

I'm a big fan of low-level programming and basically getting rid of buffer overflows and data races and those types of things. So for those of you who are engineers in the room and -- pretty great. I'm a big fan of Rust and some of the things that they're doing in the C++ community to basically move away from a lot of the old-school C memory problems that we've had. I think that we should all be doing this, so that's my little advertisement there.

I believe that lightweight security agents are a thing -- I think we're coming up to -- we're seeing more and more of those, and I think -- so we'll be able to embed agents, which is what we rely on, into the devices. At the same time we may be able to do, for ones that have a little bit more of a footprint, we may be able to do micro-virtualization, which we can even, you know, lower the attack surface even more. And, basically, this all means that the closer we can get to the guts of the matter, the greater fidelity we have for detection,

and the more likely we are to apply preventive security controls.

And, finally, my last slide, which is no matter if I'm talking medical devices with 1 person or 100 people or 5,000 people, basically I want to urge upon all of you to think hard about why we don't do application whitelisting on all medical devices, why basically the ports, processes, and services that a device -- all the ports, processes, and services that this device can do, because it's a special purpose device, it's not being used presumably to run eMacs or surf the web, that all of those should be able to be determined beforehand, that there's an update that changes it that should also be built as part of the application whitelist.

My feeling is that this is the most effective preventive security control; it's been around since the 1970s, and it is -- it can be hard, but I would urge upon all of you to think carefully about whether this is where we should put things. I know it's not a silver bullet, it doesn't solve all our security problems, but the vast majority of security problems that I see with medical devices are basically not the device; the device is just doing extra things, you know, it's doing its medical device thing and sending spam. All right. We can basically -- we can stop a lot of those if we do application whitelisting effectively, though it doesn't necessarily mean we use, you know, a product for -- but it's just something that we know what all the processes are and we restrict everything else.

And I'm more than willing for somebody to come up and say, boy, you really missed the train on this one, Darren; it's not nearly as easy as you think it is, and I'm sure it's not as easy as I think it is, but I do think this should be the principal topic, because leaving the security back to us to figure out how to come up with basically a recompiled operating system and go, yeah, the crypto looks pretty good here, I think that's just unrealistic. There's a huge shortage of security professionals, and so the likelihood that somehow or other this huge shortage is going to produce a bounty of geniuses seems to me unlikely.

(Applause.)

DR. RICCI: Thank you very much.

And now I'd like to introduce our last speaker, Dr. Seth Carmody. Dr. Carmody is a cybersecurity program manager for the Center for Devices and Radiological Health and serves as the co-chair of CDRH's Cybersecurity Working Group. The Cybersecurity Working Group is an interdisciplinary team responsible for FDA's final pre- and postmarket device guidances, and they are also responsible for incident response.

Seth.

DR. CARMODY: Thanks, Linda. Linda, you didn't mention that you are -- you are a member of said Cybersecurity Working Group.

DR. RICCI: I did leave that out; that's true.

DR. CARMODY: Okay, all right. Well, that makes sense. Seth Carmody. Totally makes sense that a Ph.D. organic chemist would be giving a talk about cybersecurity in an orthopedics device conference, so we'll see how it goes.

Slide 2.

I loved the talks earlier. I think they're right on. So why are we here? I heard a lot of problems; I heard some solutions. Just to kind of tee this up for folks, one of the -- I think one of the best things that we have right now is an opportunity in front of us. From what I understand from this group is that you're just getting started. This is a proactive group; you have the opportunity to avoid a lot of the legacy drag that we see in this space, and it starts up front with design. So can anybody tell me what the intended use of this robot is? Shout it out. I'll repeat it.

(Off microphone response.)

DR. CARMODY: Build the wall. That's a building the wall robot. Presumably, it's a nice looking brick wall. And we're very comfortable dealing with the intended use and

concepts of the intended use and concepts of this device and device ecosystem, and systems are supposed to be doing something. We're not as comfortable or familiar with designing said wall-building robot to not do certain things, and that's really the source of any of the legacy drag problems that you see in the spaces that we better focus on delivering the intended use. We've been focusing on building systems that deliver healthcare, not necessarily building a trusted tunnel through which that intended use flows or that healthcare is delivered.

So if I build -- if I research and design and develop this robot and I don't put certain protections in place and I connect it to the internet, which is very trivial to do, I have essentially opened up this robot, its engineering, and the systems that are associated with it to any adversary on the planet. I've opened up the entire adversarial space to my engineering design in this robot. So if I haven't done some very basic things, whitelisting being a great example, what's to stop this robot from hurling bricks across this factory? Nothing.

So we have an opportunity here, from design, from conception of these devices, to bake in very -- already established security principles to prevent this robot from throwing bricks across the factory, unless, of course, that's part of the intended use, which I don't know what devices you're making, but maybe you're veering off in that direction.

So let's talk about the features of an actual device here for a second. So infusion pump is a great example. It gets beaten up a lot, but it's actually a great use case for connected technology and when it's actually interfacing with a person. Some of the things I want the device to do, I want it to have drug libraries available from a server on the internet presumably. Why? Because this delivers certain clinical, say, risk avoidance. People don't have to punch buttons into a device; they can just pull the library down from the internet, which is the feature. But then at the same time, I don't want this thing to under- or over-

deliver therapy, so that communication channel has to be engineered in a secure manner, otherwise Hackerman can infiltrate that communication channel and make it do things that it was not designed to do but was not protected against things it can be made to do, which is really the essence here.

And we talked a lot -- the first speakers talked a lot about sort of the complexity in the environment. Well, here's where they are in the environment. You have FDA principally, medical device manufacturers, healthcare delivery organizations is what I would call the magical triad of folks within security. And this is really a complex environment because if you don't get things right at design or what we would call the development period or before the line or before the regulatory decision, it makes everything else infinitely harder after the line with respect to security, including procurement.

Darren has to test the device for security implementations. What is he going to do if he finds that it's not satisfactory? He doesn't buy the device. But the cake is already baked; it's not like it's going to change. It's already on his doorstep.

Deployment: These devices, can they be configured in a secure way? Operations maintenance: Can it be patched? Can it be patched in a timely manner, commensurate with risk? And what do you do when you end of life it? What are the security risks around that? Those things get infinitely harder if we don't get the design right, so it's of paramount importance to get the design right.

Those aren't the only three stakeholders; we have many different stakeholders in this environment, which makes it complex. And it's not getting any easier. Actually, lots of folks are interested in getting into the fray, but you know -- just, for example, like payers, reimbursements that are pegged to security or the security posture of devices or systems.

So what's FDA been doing? We really got catalyzed -- our efforts got catalyzed in 2013. There were a couple of things that sort of coalesced in 2013 that got us kicked off. In

2013 we had Executive Order 13636, which was basically the President calling on the 16 critical infrastructures to do better in terms of protecting critical infrastructure, and guess what? Healthcare/public health is one of the 16 critical infrastructure sectors.

Secondly, we had a couple of recalls here; they started around 2012 and '13 but sort of came to prominence officially in 2013 or were classified in 2013.

And then, thirdly, we had a security researcher drop about 300 different devices with about 10 different vulnerabilities each into our laps, and we had no formal process or mechanism to deal with that type of information; hence, the Cybersecurity Working Group got started in 2013. That group is responsible for the policies that you see here in 2014 and '16, final pre- and postmarket guidances, which basically outlined our policy, total product life cycle policy for security and medical devices, and we've had numerous learnings along the way, including things in 2018 which 4 weeks ago when I was generating this updated slide for 2018, I was like, hey, it's 2018, we need a 2018 dot. There it is. But it's so crowded, I couldn't even put the accomplishments already in 2018. I'll get right on that, I assure you. But, yes, we have a long history that started in 2013.

I'm just going to outline some of the policy, the policy highlights for premarket cybersecurity. One, it was the first time that we said, hey, this is a shared responsibility; this is a complex ecosystem. We can't, as medical device manufacturers, say in our contractual language when these things are procured, hey, by the way, when you hook this thing up to the internet, it's totally your responsibility in terms of security. That's not a palatable long-term solution, so it's really a shared responsibility primarily between FDA, medical device manufacturers, and healthcare delivery organizations.

Secondly, you address cybersecurity during the design process for reasons that I already outlined.

And, number three, these are tied to existing authorities, including design inputs or

design controls.

Very quickly, the postmarket guidance, final in 2016, really said, hey, you know, we need a methodology for handling risk in the postmarket, and these devices can't live for decades in the postmarket sense because they're still safe and effective and they're clinically useful. It doesn't matter if they're running MS-DOS because they actually deliver good healthcare. That's the reason they're still clinically effective. But we need a risk framework for managing this to determine when it's time to actually upgrade, so that's what we put out.

We also wanted to articulate further, under the quality system, what our medical device manufacturers' responsibilities were. And then really importantly, not just -- to authorities, is create a culture of collaboration and coordination, because it was so complex, there was really no other way to go about it. This includes information sharing between folks who are not very comfortable sharing information with each other.

So I mentioned before we're an executive agency; therefore, we should align with executive orders, including the NIST framework coming out of NIST. And then incentivize right behavior; what are the structures that we can put in place to get people to move in the right direction that's non-punitive, non-compliance, but actually drives great security?

So here is the outcome of that, that risk matrix. You may or may not be familiar with this, but basically ISO 14971, the concept of harm, we took that and made a patient arm and scoped it down. You're familiar with that. The concept that folks may not be familiar with is exploitability; what is the actual sort of feasibility of exploiting any one particular series of vulnerabilities? Well, here it is, leveraging the concepts borne out of the Common Vulnerability Scoring System, which is a standard and calculator based of the FIRST organization, and I forget what FIRST stands for. It's a collection of CERTs, CERTs being the Cyber Emergency Readiness Response Teams.

There are three components to the CVSS score: a base score, vulnerability specific, the parameters of the vulnerability; there is a temporal scoring risk that changes over time; and then an environmental score. What is your device doing to knock down the risk? You can go learn about CVSS on their website. That's how I learned about it; they have a very good compendium document or a companion document to the calculator, and they'll explain everything.

And then, finally, here is the concept that we've been putting out in terms of how you manage or think about cybersecurity risk in the postmarket sense. If there is any risk of patient harm or if there are no risks of patient harm, are there risks of patient harm due to any particular vulnerability? As such sufficiently -- well, either there's none or you have sufficient controls in place. We say, hey, go ahead, change your device and response to risk. Even it might be business risk or reputational risk or whatever, financial risk, we want you to go do that.

In fact, we want you to go do that so much that we're going to remove any regulatory barriers, meaning that you don't have to come in to the FDA under most circumstances to have that device re-reviewed. So if you want to do a software update, go do it. Security only, go do it. We don't need to review it, we don't need to recall it; just go do it.

If you judge the risk to be sufficiently high and not controlled, meaning the risk of patient harm and there aren't sufficient controls in place to knock down that risk in any measurable way, we have also given you a regulatory incentive to avoid coming to the Agency, and that is that you have no adverse events. Nothing that has happened because that's being proactive; I'm fixing something before it happened.

Two, that I remediate within a certain time frame; acting fast is good. Why is that good? Well, how fast should you act when you have a safety concern? As fast as you can;

that's the answer.

And, number three, sharing information broadly with the sector because your problem may be other people's problems. WannaCry was brought up, a set of problems that were shared by folks. Sharing information around that issue, how you're fixing it, would be immensely valuable.

If you do those three things, you actually avoid having to come to the Agency under 21 C.F.R. 806. You can go fix it, communicate to your customers in a timely fashion, and this is not -- it's considered a correction removal, but you don't have to report it to the Agency. So that's what we did.

We also said, hey, you know, we need to do good things, and we need to incentivize good things, so calling out folks -- calling out to folks that there are concepts such as cyber hygiene. You know, let's enable people to do security updates without having to incur regulatory penalty so that you can make changes to devices without coming in to the Center, as I already mentioned. There are some stipulations in the guidance. Go ahead and take a look at that, annual reporting requirements.

All right, I think I win for the most words on this one, on any particular slide in this group here. I won't go through this ad nauseam, but you can check it out. It's in the postmarket guidance, but basically it's saying, as I already stated, if no adverse events, you remediate in a timely manner, and you're communicating those risks broadly to the healthcare/public health sector, you don't have to report those corrections or removals to the Center. There are some reporting requirements under annual reporting; I encourage you to check those out. But, in general, this is our -- covers our incentive structure.

Thank you. I guess we don't do questions now. We'll do them on the panel. There's a panel right over here, so we'll do that. All right, thank you.

(Applause.)

DR. RICCI: Thank you, Seth.

I want to make sure that, you know, as we go through this panel discussion, that you all are involved, so I encourage you, if you have questions, to come to the microphone, you know, wave your hand, and be active in this discussion. So anyone?

(No response.)

DR. RICCI: Well, I'll start. I wrote down a bunch. So, Seth, because I'm on my page of questions --

DR. CARMODY: Uh-huh.

DR. RICCI: -- for you, what do you think that manufacturers can do to encourage good hygiene throughout not only the development but once it's deployed?

DR. CARMODY: Beautiful question, Linda. One of the things that we see as most impactful at a manufacturer organization, and it sort of gets to your point but in a more generic way, do you have somebody that's the most responsible for security at your organization in terms of the engineering? So what we're highly recommending folks to do, if you don't already have one, is to go out and find -- I don't know if they exist per your 12 expert comment -- a product security director that's going to be developing a team to go out into the portfolio, your business portfolio, product portfolios, to build security into the device such that they can be implemented, they can be deployed and configured and updated once they're sold. Otherwise, I don't see any other way to bake in security into the design to enable the things that you're asking.

DR. RICCI: Thank you. And kind of on that same line, Salwa, can you discuss how do you think a company should begin when they're trying to define what their attack surface is for their device?

MS. RAFEE: That's a great question. You know, companies should start looking into an overall cybersecurity strategy first. This is the thing that they need to start with,

assessing the risk, making sure that they're aware of what they have in their environment, and really, we talked about the culture, security as a culture, security as a hygiene and a practice. It is an everyday practice to the employees and the practitioners, looking at that and trying to hit, you know, the compliance and regulations.

But it's an ongoing security and compliance procedure, looking at every single layer of the organization, from the networking, the infrastructure, the application, and the data, how we can maybe perhaps move their data to the cloud. Maybe this will provide more regulation, more innovation to their main line of business and all the security controls that need to be adopted within the organization. So it is a closed-loop kind of environment, continuous, providing negative feedback so that we can adjust, eliminate all the false positives, and really using the state-of-the-art solutions that we have now. We talked about orchestration and automation of the security solutions.

You know, the rest of the speakers talked about the shortage of the security skills. We don't have enough to cover all of these threats that come from burdening our organizations, so we have to do automation; we have to orchestrate all of the solutions within our organization to be proactive and adaptive to what we are encountering. Thank you.

DR. RICCI: Thank you. And then kind of tying those two things together, because one thing that I am hearing from both IBM and from the Agency is the need for companies to be engaged in security from the get-go and really understand what their device is and understand the weaknesses that could be present.

So now, Darren, I want to turn to you and ask you how you see this from a healthcare provider stance, how you see this evolving once the devices have been delivered to the hospital and are in the hands of caregivers.

MR. LACEY: Okay, I did want to answer the other question, though, quick. Check

your libraries; third-party libraries would get you half the time. So that was my bit of advice.

But once you get to us, the -- I will say that, in the last couple of years, the manufacturers have done a much better job in providing security capabilities to their products, I mean, just really much better than a few years ago. The problem is that we're still at the phase where you haven't figured out -- manufacturers, like most of you aren't manufacturers, so we say they haven't figured out, and we haven't figured out which ones actually work and which ones don't in the enterprise environment, so it's sort of a natural state of evolution as we sort of go through this.

I would say, though, you should always assume that the people that you're selling this to, even the security people, don't know a lot about security, that pretty much operate, you know, it's like, well, they probably know how to turn the computer on and then don't go much beyond that, because if you start thinking, oh yeah, they're going to basically do the segmentation and then they're going to create this and that and the other thing, a good portion of that time we're going to screw that up; we're going to do it exactly wrong and create actually more problems.

So one of the things you want to do is you want to basically go in, both with respect to the documentation and the security capabilities, go in with the idea that (1) you need to make them the default, because if they're not the default, we won't deploy them; and (2) that they're idiot-proof or close to it. And if you can't get there on either of those, it's okay to try it out on a few, you know, as you're trying to work through that, but that should always be the goal. Really, you know, I think overestimating people's security acumen is one of the biggest problems our whole industry has right now.

DR. CARMODY: I was going to add to that excellent point, and it gets back to the concept of shared responsibility that -- well, Darren, you're here. I'm going to invite you to,

if you're interested in finding out what your user requirements are, come talk to this guy; he already gave you a few of them, but really establish, you know, who your customers are, who's going to be deploying them so you can figure out what you actually need to do instead of making guesses or making assumptions, because as Darren already pointed out, that will be problematic.

DR. WOODS: So I'll throw this one out generally to everybody. Seth, maybe start with you. You mentioned security researchers and somebody dropped like 300 different device vulnerabilities on you guys in 2013, and it led to this, you know, kicking off the working group. There's been a sharp increase in the number of security researchers looking at medical devices and finding things, and I know that that's -- that can be a polarizing thing in this community. So from your perspective, security researchers, are they part of the problem or part of the solution?

DR. CARMODY: Yeah, great question. In our postmarket guidance we put out in 2016, we called on manufacturers to have a coordinated vulnerability disclosure policy, which basically is the rules of engagement for security researchers when they find vulnerabilities in your devices, and in general, we put that out because we believe that engaging with security researchers is a positive thing. They're coming to you with essentially free pen testing and in a way and as a signal to process, to figure out, you know, how good is our security. So it's, in general, a good thing.

The coordinated vulnerability disclosure policy that you have, and you can -- there are a number of examples which you can draw from publicly available, which will sort of govern the rules of the road and rules for engagement when you're working with folks that may not ever have interfaced or worked with a huge company that you may be in. So it's just a good way to say, hey, we're accepting outside information; we will work with you at setting expectations, but here is the main value to having a coordinated vulnerability

disclosure policy. It aligns you internally to security information. It gets everybody at the table, if done right, to sign off on saying, hey, yeah, we have a way to deal with external security information. To date, there are 14 companies that have public disclosure policies. I think there are over 13,000 medical device, registered, listed medical device companies. It would be very beneficial for you to align internally to know what to do with security information, legal, quality, regulatory, you name it.

MS. RAFEE: So, you know, I don't think the security community is to be blamed here, you know; there are the factors of speed, scale, and complexity of the cyber attacks that the security analysts cannot keep track of all of what's happening in any given organization. You know, the hackers are one of the -- this group of the best programmables. They have the best tools, they are very sophisticated developers, and they keep with the innovation part of their -- as I mentioned, you know, the ransomware and the service, all of the software, they keep bombarding the organizations.

You know, the enterprises, the providers, payers, and life sciences, in addition, they need to invest more in having those solutions and not just in the -- you know, we don't wait for the incident to happen so that we can have an incident response solution. We need to think ahead of time about the integration of policy, people, and technology so that if or when an attack happens on the organization, they are immediate to react and mitigate the risk. So, again, moving the mentality of, you know, compliance to just a risk-based approach is really the best thing that any organization should take into protecting and having a layered security solution.

DR. WOODS: All right, so I want to kind of flip something around really quickly. We've talked a lot about what device makers and healthcare providers can and should do with medical device security, but I wanted to see if we can elicit one, a single characteristic that when you see it in a medical device either that you're looking to procure or evaluate or

whatever, that when you see it, you cringe because maybe it's going to make your budget for that project explode or maybe you're going to have to dig in really, really deeply. So what one thing, just going around the forum, would you say most kind of triggers that cringe response when you see it?

MS. RAFEE: So that's a good question. I think if I see a device with the Windows operating system, I cringe immediately because I think immediately that it needs to be patched and it needs to be up to date with that. Also, the second factor is being active, like being part of a closed loop, so it is on the high risk of life-threatening situation if it happened to be counterfeited or spoofed or impersonated so that we have a bigger focus on these devices.

DR. CARMODY: Could I soften your cringe declaration?

DR. WOODS: Sure, I'll allow it.

DR. CARMODY: Okay, great. So what I expect to see in a mature device company is signed firmware, software, the ability to be updated securely. I think there's a discussion for whitelisting, and then third-party testing goes a long way as well, so those are the types of things we like to see.

DR. WOODS: Darren, any thought on that from you? And then we'll go to the question.

MR. LACEY: Yeah, if I see the Linux operating system, I get nervous. Actually, I mean, right now there's -- not everyone does WPA2-Enterprise, and so if you don't support that, in most sophisticated healthcare environments, you're going to cause problems because of the way we configured our wireless networks. This is something that just basically -- I know you all -- they all want to do it and they all will do it; it's all in their -- on their plans, but whenever I see that, I'm like, oh yeah, this is going to take a while.

DR. CARMODY: I think we inspired some people.

DR. RICCI: Yes.

UNIDENTIFIED SPEAKER: Oh, hi there. I might even be more paranoid than you are because I'm wondering about your flowchart that showed does this device impact patient safety, and I can even imagine situations where the automatic paper towel dispenser can be -- if it's connected to the internet, can be used to, say, spoof other things and cause harm. So the question is where do we draw the line on any of these devices?

DR. CARMODY: Yeah, great question. I think I'll try to explain it in the concept of a trust boundary, like what is the device that could cause the most harm to a person, like so how far away from an actual patient. And that sort of puts you sort of on the same Class I, II, III in terms of risk, but the things that are also connecting to it and talking to it.

So I don't know what devices you're building, sir, but if the paper towel dispenser is talking to your medical device, I don't know. Maybe you guys are working on that right now, but -- for whatever reason. But if that is a communication channel that you deemed appropriate for your market, then the paper towel dispenser should not be able to tell the device to drop or to dispense its entire therapeutic cartridge or, you know, whatever it is, so what are the appropriate protections to put in -- what are the appropriate protections to put in place in that communication channel? Should it be listening and changing therapy based on talking to the paper towel dispenser? Probably not.

UNIDENTIFIED SPEAKER: Right.

DR. CARMODY: I don't know.

UNIDENTIFIED SPEAKER: We don't make paper towel dispensers, but my point is that somebody does, and somebody's going to connect them to the internet, and now that becomes a medical device --

DR. CARMODY: Yeah.

UNIDENTIFIED SPEAKER: -- if it's simply in the area where the rest of our devices are

because they can always --

DR. CARMODY: Yeah.

UNIDENTIFIED SPEAKER: -- spoof up a channel and interrupt communication between anything else, right?

DR. CARMODY: Yeah. I'll probably very quickly step outside of my expertise comfort zone, but one of the things I talked about in terms of signed firmware or signed updates is using cryptography as a tool to establish trustworthiness between two nodes, right? So if I'm a device and I'm interacting with a patient and I'm delivering therapy and I'm dependent -- and the patient is dependent on that therapy, and we can have all sorts of discussions about, you know, how high the risk goes, am I supposed to be listening to you, am I supposed to be acting and not verifying that you're actually something that I should be taking a command from? That's where we want folks to move. Instead of implicitly trusting that I'm supposed to be acting because this is my programmer, it's telling me that I'm supposed to do that and I haven't verified that it actually is the programmer using security principles, then we need to move from implicit trust to a trustworthy system, and there are ways to do that.

DR. RICCI: And I'm not part of the panel exactly, but I can't help but give my opinion. So I really like your question because it brings together a bunch of points that have been brought up about defining your attack surface, for example. Where could somebody attack your system, and then going into the risk analysis that was done for the devices and the device manufacturers should do as well and understanding, you know, what could happen, what bad things could happen as a result of the weak points that someone could attack.

So, you know, as Seth was saying, if someone can change the parameters on your device based on, you know, a wireless input or an input from some other source, so that's a weak point, so how are you going to secure that, and what are the implications if that's

wrong or you don't know who is doing that? So that's gathering all of that information about, you know, where your device could be attacked and what are the clinical implications of such an attack is how you go about understanding how secure your device is and making the appropriate judgments and including things like cryptography at the right time.

DR. CARMODY: Yeah, just to add on to that, you probably are already really good at identifying what your clinical hazards are, and really what you're trying to do is connect how can an adversary, a threat, manifest those same clinical hazards but through -- and secure me, an insecure channel.

DR. BAUMANN: We do have an online question; this one's for the group. Do implant device readers use standardized secure communication protocols? Maybe?

DR. CARMODY: Maybe. I don't think I could say, even if I knew, and I might know but -- I'm not comfortable answering the question.

MR. LACEY: Are they saying has one ever been invented that did, because I think so. I mean, I looked at a few that looked like they were using what I would consider reasonable, you know, communications protocols, but it's possible that I was wrong and misread what I was reading. But, yeah, that one's a tough one.

DR. CARMODY: I think, in general, medical device manufacturers use proprietary protocols, the security of which would have to be evaluated on an ad hoc basis.

MR. LACEY: Yeah, true, but I did some with standard, you know, standard communications protocols.

DR. CARMODY: Sure, absolutely.

MS. RAFEE: If I may add, you know, this is really what we need to get done. We need to look at the framework; we need to look at the platform for IoT devices and really define the standards that we would hold all the manufacturers responsible when it comes

to medical devices. Right now, we are getting lots of these medical devices, you know, I'm just going to set an example, made in China; we have no idea how they were manufactured or the encryption level or the code itself, if it has been scanned for vulnerabilities, or not and everybody's using them. Sometimes patients come to the hospital already fitted with these medical devices. So right now this is the -- you know, we are -- you know, the timing is right when we are faced by this evolution of the IoT is to define those standards and really warn against the life-threatening situations that would come if not standardized.

DR. DMITRIEV: Anton Dmitriev from the FDA. I think Ms. Rafee just answered one part of my question, and that is with tens of thousands of manufacturing facilities worldwide, just for the medical devices alone, and a majority of electronics being manufactured overseas for the cost effectiveness, how can we control sort of the validity and/or integrity of these circuits that we're trying to either create or incorporate into medical devices? That's one question. Maybe you could just -- the panel could elaborate on that just a little bit.

And the second part is what about data integrity, period? So we are going to spool and/or upload terabytes of data into the cloud from the various types of devices, and we will rely on this validity or integrity, basically natural organic state of that data. What if there's an intrusion and basically malicious intent to modify the data? How do we protect and how do we basically maybe advise healthcare providers and manufacturers who are interested in taking off-the-shelf SMART devices, such as Fitbits and otherwise, and incorporate them into clinical care continuum; what certain steps need to be taken in order to ensure data integrity? There's been a recent case, maybe a couple months ago now, that there was a group of young enthusiasts that have uncovered secret U.S. military bases worldwide just by virtue of service members wearing Fitbits or other like devices during their morning runs and PT routines.

MS. RAFEE: You know, I will start here, Anton. This is a great question. It's a very complex ecosystem that we are faced with. I'll give you an example. You know, I was in Australia a few months ago, and some of the states in Australia and actually some of the Nordic countries have designed genetics banks for the entire population, and they are putting all of this data in a cloud. I mean, imagine the international security if any of this data has been breached; this is your population genetics information, and all of this data will be in the cloud at some point in time. So securing this data is a mandate.

Again, the counterfeiting of the medical devices, some of our researchers working on several projects, you know, discovered -- and it might be a simple example, the HIV strips that have been manufactured here, they are using for positive or negative, these have been counterfeited to be used for pregnancy testing, and they are sold -- you know, everything has been repackaged and sold as pregnancy testing strips. So it just shows you how easy things are being sold in third world countries. The level and the attack surface here is almost endless, so precautions have to be taken, and really, we need to think as a community about all the measures that will be taken, have to be taken to prevent that.

DR. CARMODY: So I'd like to flip that question back around on our audience, and that's what we're asking folks to do, is that you have to consider from a design perspective if the data is corrupted or not integral in some way, what does your device have in terms of protections on it such that it will or will not react when presented with data that is not integral or authentic? So it's really a design consideration in the threat model. You should be considering that very situation on your design.

UNIDENTIFIED SPEAKER: Hi. I'm wondering if FDA considers patient data privacy a patient safety concern?

DR. CARMODY: As defined in our postmarket guidance, no, but we do think it's important; therefore, our policies reflect its importance. So to drive home the point on

what we consider patient harm in the postmarket guidance, we specify that as physical harm to a patient, with respect to privacy, which is really the Office of Civil Rights at HHS, their domain. But specifically from a design perspective, that if there were a privacy breach, just use a very general term, there's no reason -- our policies actually incentivize fixing a device design or a system design such that you can remediate that type of issue with very little regulatory penalty. Basically, you can go fix the device; it's a security only issue -- I'll put it there, for example. So that's what we -- we try to thread the needle there and to enable folks to fix problems that may be privacy related but specifically scope out where the FDA had concerns of direct patient physical harm divisions.

DR. WOODS: So one thing I'll throw out there in response to a couple of the last questions is I was at a Heart Rhythm Society event, and somebody asked a question, they said -- or made a point. They work at the VA hospital, and some of the veterans would come in, especially those who had been in service overseas, and they were refusing to have implanted defibrillators or pacemakers, which would literally save their lives, because they were afraid of some adversary who was potentially tracking them and could then do them or their family harm, who could potentially change information in order to do them harm or falsify records or to actually physically kill them using the pacemaker device.

So whether or not the FDA is looking and scrutinizing a lot of these things, there's going to be a public perception issue, and especially, I think it's appropriate for this crowd, thinking about orthopedics, since a lot of your patients are disabled veterans, particularly they'll have issues of PTSD and things like that. So it might not be the things you're doing within those devices; it might be perception of the things you're doing within those devices and with any kind of a cloud infrastructure to keep that patient data safe, private, and integral.

DR. CARMODY: Just one add-on, you know, the policies that we put forth -- well, I'll

say the premarket guidance, you know, the concepts in there could easily get you privacy as well.

UNIDENTIFIED SPEAKER: So we've talked a lot about specific controls, and we've used terms like design input and threat modeling. And there's a lot of industry efforts going on in these spaces to help build frameworks and help educate and help some of the smaller and midsize companies that may not be as experienced in this space. I know FDA's been participating in a lot of this with manufacturers and hospital providers and others. And I was wondering, Seth, if you could maybe talk a little bit about some of the industry initiatives that are going on to really help collaborate and move the needle in healthcare cybersecurity.

DR. BAUMANN: In the interest of time, can we make it our last question? Thank you.

DR. CARMODY: Very well. I better answer it well. Yeah, I'll just point one in particular out. Colin, feel free to correct me. So right now, as I said in my opening talk, what we really need here is a collaborative solution. It's a complex ecosystem with big problems, so therefore, we need to work together to solve those. One of the things that is going on right now is within the -- it's called the Joint Strategic Plan. It's coming out of the IGCC -- GCC/SCC working group. I think it's being spearheaded by the SCC, which is the Sector Coordinating Council. It's a group of private sector companies that are basically saying, hey, what is taking some recommendations from the Health Care Industry Task Force, Cybersecurity Task Force, and saying what can we do for our industry and guide them to what good security looks like in a medical device manufacturer? So that's an effort that's going on right now, putting together a Joint Strategic Plan, which is basically a guide to the industry as medical device manufacturers and deploying those medical devices within the healthcare delivery organization enterprise. And I don't know if there's open involvement,

but I can follow up and get folks that information, if you're really interested.

MS. RAFEE: Can I add just a small thought, that in addition to the strategy and the controls, I think really the marriage between blockchain and cybersecurity solutions will really add lots of value to all medical devices. You know, the blockchain will provide authenticity authentication and traceability of each device, so we need to adopt that, and the cybersecurity solutions will be able to protect the whole dataflow, the workflow of a medical device. So I would recommend that, you know, I think FDA is looking into that, and the two big domains will have to really overlap so that we can have at least solve 80, 90% of these problems that we are seeing here.

DR. RICCI: So I want to take this time to thank all of the speakers and my co-moderator. This has been a great discussion. I really appreciate all of your time and efforts.

(Applause.)

DR. BAUMANN: Thanks again to our cybersecurity panel. We're going to take about a 10-minute break. We're still running a few minutes behind, but we are having some great discussions, so we certainly don't want to squander that. If we can come back and get started again with our last session of the day at about 3:30, that would be fantastic. Thank you.

(Off the record at 3:22 p.m.)

(On the record at 3:33 p.m.)

DR. SOVES: Great. So hello, everyone. My name is Connie Soves. I'm one of the regulatory advisors for the Office of Device Evaluation in CDRH. I'm here with Janice Hogan from Hogan Lovells, who is a very experienced consultant to the medical device arena. We have the privilege of moderating the final session of today's wonderful workshop about regulatory considerations for these devices with SMART technology.

So, with that, we'll invite our first speaker, Michael Owens, to the podium. Michael is one of the co-organizers of this workshop. He has a background in computational biomechanics and joint arthroplasty. He joined CDRH over 10 years ago and has experience in both pre- and postmarket review of medical devices.

Thank you, Michael.

MR. OWENS: Thanks, Connie. So I'm not sure I'm going to be able to compete with Darren as far as the visual elegance of my presentation, but I can 100% guarantee that I will be talking about the most interesting topic of the day, U.S. medical device regulations.

So, actually, I want to go back to my first slide. So what I hope to do is kind of cover regulatory overview and provide some details on regulatory pathways, and I hope, for those in the audience and those online that are new to medical device development, that this will provide you with a foundation on which to build your knowledge. And for those of you that already have this foundation, I only have one request, and that is to keep your snoring to a minimum.

(Laughter.)

MR. OWENS: All right, so Ed stole my thunder on these first couple of slides, but I'm sure he won't mind if I go over them again. Right here I have the definition of a medical device; it can be found in Section 201(h) of the Act, and it is essentially any article that meets the three criteria I've listed here for which does not achieve its primary intended purpose through a chemical action nor is it dependent on metabolization.

So now that we have an understanding of a device, I'm going to go over our mission statement, which I pasted here. Ed kind of alluded to it earlier, but what it boils down to is that it is our mission to protect and promote the public health. But there are two other points that I want to concentrate on, again, reiterating what Ed brought up, and that is, first, that it's our commitment to patients and providers to have timely access to medical

devices, and also the second point is, is that it's actually in our mission statement to facilitate medical device innovation, and I hope that sticks with you. And I'm sure Ed, if he's in the room, is really going to like this because I'm going to talk about OSEL some more.

So, first, the way I set this up is basically following the total product life cycle, and the first office I'd like to highlight is our Office of Science and Engineering Laboratories. As Ed mentioned, their job is to make sure that we never have to say "I don't know," but what I want to point out is that early in your device development, the Office of Science and Engineering Laboratories is a valuable resource.

In regards to facilitating medical device innovation, OSEL collaborates with all of our stakeholders, and they realize that a large percentage of medical device companies have short staff and do not always have the resources to dedicate to developing testing methodologies, so they are always there to engage early in your device development in order to create these methodologies prior to submission to the Agency.

Now, when you're ready to submit your application or submission to the Agency, the second office I'd like to highlight is our Office of Device Evaluation, and ODE is responsible for the program areas through which these medical devices are cleared, approved, or granted. And what I've listed here are the major program areas that ODE is responsible for, and I'm going to touch on a majority of them.

But before I do that, I quickly want to go over device classification. We classify devices based on risk and the amount of regulations necessary to assure safety and effectiveness, and we break that down into three classifications from low to high risk, as you see here. For Class I devices, they are lowest risk devices and typically do not require FDA premarket submission. They are generally -- can rely upon general controls to provide a reasonable assurance of safety and effectiveness, and I've included some examples of general controls here, rules for adulteration and misbranding as well as GMP rules. I've also

included a simple orthopedic example here, which is some, some -- and I stress "some" for those out in the audience, some medical device instrumentation.

The Class II is for moderate risk devices, and for these devices, general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness; however, it has been established that special controls can provide that assurance. Special controls are typically device-specific, and some of the examples I've included here are performance testing, biocompatibility testing, stability and shelf life testing, as well as sterilization. And some of the orthopedic examples I have for Class II devices are the fixed bearing knee replacement and a total hip replacement.

And, finally, our highest risk devices are our Class III devices. For these devices, insufficient information exists to determine that general and special controls are sufficient to provide a reasonable assurance of safety and effectiveness. They typically require a PMA and include such things as quality systems review and inspections. Some examples in the orthopedic realm for them are total disc replacements, and that is a mobile bearing knee.

If you have any questions about what classification your device belongs in, you can submit a 513(g) to the Agency, and they will provide you with their views about -- with our views about classification and regulatory requirements. Information on 513(g)s can be found in the link below.

So now let's move on to the premarket notifications or the 510(k) program. The 510(k) program is an evaluation of substantial equivalence to previously cleared or pre-amendment devices, and the date to remember for pre-amendment devices is May 28th, 1976, and the information -- I was getting some approval from Mark and Raquel over there to make sure I got that date right. Information on what to submit in a 510(k) can be found in 21 C.F.R. 807.87 as well as the link below. And the key here is substantial equivalence. Most orthopedic devices are reviewed within the 510(k) program.

If you are considering whether your device is a 510(k) device, you're going to want to take a look at this chart here. It can be found in Appendix A of the 510(k) substantial equivalence guidance, and it basically goes through all the important decisions that we go through, all the important questions that we ask and the decisions made to demonstrate substantial equivalence.

But for the purposes of today's talks in SMART technology, I want to concentrate on two questions, and the example being say you have a 510(k) device, let's say a total knee replacement and you want to add a sensor to that total knee replacement. How would you answer these questions? How would you answer, does the device have the same intended use? And if you make it past that question, how would you answer this question: Do the differences in technological characteristics of the device raise different questions of safety and effectiveness?

Now, what about products without a predicate that may be low to moderate risk? The de novo process is a classification process in which you believe that general and special controls can mitigate all the risks associated with your device; however, there is not a legally marketed predicate. So what you're going to want to think about in this case is can I identify general and special controls that will mitigate all the risks associated with my device? Information on the de novo process can be found in the link at the bottom of this page.

And, finally, our premarket approval program. This is the process through which we review our highest risk devices, and they typically require clinical data and a GMP review and inspection. Also, a summary of safety and effectiveness is prepared and made publicly available. Information on the premarket approval process can be found in the link below.

I'm doing really good on time.

So if you think that you need a clinical study to support your device, you're going to

want to consider -- and you want to conduct that study in the United States, you would need to potentially conduct an IDE study, and the important thing here with sensors is that, we're going to talk about later, is how and who you show that data to while you're evaluating it? And the studies required are based on risk; for example, for nonsignificant risk devices only require IRB approval, but for a significant risk device, you would require FDA and IRB approval.

Now, I realize that our regulatory process can be complicated, so I want to emphasize our Q-Submission program to wrap up the Office of Device Evaluation. Q-Submissions are a mechanism for requesting FDA's feedback prior to premarket device submission. It's a valuable resource for both us and the medical device community.

Now I want to concentrate on pre-submissions for the first today because I think that there is a lot of great value in that in bringing a new technology forward. So I'm going to read each one of these points so that all of my friends in the audience can appreciate the GIF that I found. If you've ever come in to this, the FDA, for a face-to-face meeting for a pre-sub, I hope you get a kick out of this GIF. But there's a lot of reasons and advantages to submitting a pre-submission, including the introduction of novel technology, design of a clinical protocol, discussion of specific preclinical data or testing approach, and discussion of upcoming submissions.

With that being said, when you submit your questions in the pre-submission program, FDA will submit -- will provide you with comprehensive feedback, but please understand that that represents our current thinking, which is very important in a rapidly devolving -- rapidly devolving -- rapidly evolving space like SMART technology. What I've included here is a table of some examples of good pre-submission questions and bad pre-submission questions. An example of a good pre-submission question would be is the specific animal testing plan adequate? An example of a bad pre-submission question, a

very, very bad pre-submission question is what do I need to do to get approval?

So, finally, as you're moving -- your device is now on the market in the total product life cycle, the Office of Compliance's mission is making sure that they ensure compliance with medical device laws, and why do they do this? Because there are multiple provisions in the Act for postmarket requirements. Some of the things that the Office of Compliance is responsible for doing are listed here. Examples include reviewing certain device manufacturing site inspections and review of postmarket corrections or removals or recalls.

My Office of Compliance colleagues have provided me with these four take-home points for you to consider in the postmarket, but for today I'm going to concentrate on the second and third.

The second one reads, "Do changes made to your firm's device, including labeling, require a new premarket submission?" Now, imagine that you have a SMART device that includes a graph, a simple graph, but you want to add information to that graph because you can determine that there's additional correlation. Would the addition of that information that you're giving the doctor require a new submission? That's something to think about.

And in regards to the third question, "Is your device labeling truthful and non-misleading?" now are the instructions for the doctor, for their interpretation of the graph that you are providing them, is it supported by evidence? That is also something that we're going to want to see when reviewing these devices.

And, finally, CDRH has many excellent educational resources for the information I just provided you, and if you have any specific questions for orthopedics, I've left the number for the Division of Orthopedic Devices; it goes right to Mark's office.

And with that, I'll end. Thank you very much.

(Applause.)

DR. SOVES: Thank you, Michael.

All right, so our next speaker is Joshua Chetta. Dr. Chetta is a biomedical engineer in the clinical trials program in FDA's Office of Device Evaluation in CDRH. For the past year he has worked as part of an inter-office team developing processes and resources for staff to help CDRH implement the real-world evidence guidance document.

DR. CHETTA: Good afternoon. Thank you for inviting me to speak. Michael just gave you a great overview of kind of how the Center approaches device regulation based on risk. Inherent in that kind of risk evaluation of devices is the idea of the technology in the device and how the device is going to be used. As he mentioned, depending on that risk, not all devices are going to require clinical evidence to support regulatory decision, but for those that do, say it's got a novel technology or new intended use, I'm going to talk about a few, so four different programs or initiatives that the Center has to help programs and initiatives that the Center has to help companies kind of develop high-quality clinical evidence to meet a particular regulatory need.

So we'll start with Investigational Device Exemptions. The IDE, or Investigational Device Exemption, really is trying to balance the kind of inherent tension in the mission of the FDA, which is to promote and protect public health. On one hand, we want to make sure that patients and subjects and research are protected, but we also want to make sure that we are supporting and kind of helping to spur device innovation.

And so what the IDE regs do, this is in 21 C.F.R. 812, they allow devices, so it's an Investigational Device Exemption, it exempts investigational devices from certain regulatory requirements that they would otherwise -- that legally marketed devices are subject to, and in particular, approved IDEs are exempt from regulations pertaining to the following: The IDE regs apply to clinical investigations to determine device safety and effectiveness, and this includes both investigation of a brand new device but also investigation of new uses for

legally marketed devices. And this can include a wide range of different study types, everything from potentially an academic study that's very basic in nature through, say, feasibility studies all the way up to what we think of as kind of a large, traditional pivotal study supported by a sponsor/manufacturer in order to support a future marketing application.

And because of the kind of breadth of the types of studies that could be conducted, we classify these not based on study type but by study risk. And study risk is a contingent -- or is a composite of how the device is going to be used as well as the device technology. It's not just a -- the study risk is not made just based on the device alone. There's three categories of risk: significant risk or SR; there's nonsignificant risk or NSR studies; and then, lastly, there's exempt studies.

Significant risk studies are subject to the full requirements, full IDE requirements. These are devices which present a potential for serious risk to the health, safety, and welfare of a subject.

Nonsignificant risk studies are those device studies that don't quite meet that definition. They're subject to abbreviated requirements, which means that there's somewhat less reporting and they don't have to come to the -- and those studies are not required to be approved by the FDA prior to initiation; they only have to go to the IRB.

And then lastly exempt studies, there's a list of seven exemptions under 812.2(c). These studies don't require prior approval by the FDA either; just go to your IRB. Examples that I think would be interesting to members of this audience, commercial devices that are being studied in accordance with their approved or cleared labeling are exempt from IDE regulations, and also some types of in vitro diagnostic devices are also exempt from IDE regulations.

I mentioned IRBs. IRBs play a very important role in initiation of clinical

investigations. They are the first line in helping sponsors make determinations on study risk. If there are questions or uncertainty, we always encourage IRBs or sponsors to come speak with us. We're here to help, and we can make the final determination on a study risk.

And then before I move on, I want to just highlight some common pitfalls for submissions. In general, if we don't have adequate information to understand either what the device is, how it's going to be used, what the study is, why the study is being conducted, or how you're going to make sure that you're protecting patients or subjects in that study, those are going to be things that we're going to ask questions about.

Early feasibility studies are a subset of IDEs. These are studies where you basically exhausted kind of all that you can -- or extracted all that you can from kind of bench and animal testing; you really need to get the device into a human in order to gain additional understanding and kind of drive that innovation further.

There's a voluntary program for devices in very early stages of development to be studied in a small human clinical study. It's basically a standard IDE, but we recognize that because the devices are so early in development, there's going to be quite a bit of unknowns about how the device is going to perform. And, again, just to highlight that it's -- this is going to be a small number of subjects.

There's an informal designation, so everything is basically normal, but we do have additional kind of resources in the Center, so an EFS representative, and you can also expect additional interaction with your review team if you're submitting an EFS IDE. The submission is normal, but we recognize that there's going to be significant questions about the risks, and so we're going to be looking for kind of a pretty comprehensive approach to how you're going to mitigate those risks given kind of all the uncertainty around the device. And then I'll highlight this last bullet as well, that one of the nice things about this is that there's mechanisms to kind of accommodate the expected device iteration, again, because

we recognize that this is very early in development.

The Breakthrough Devices Program is a little bit more comprehensive and formal process than the EFS. Where EFS was just an IDE, the Breakthrough Devices Program is really trying to encompass the entire spectrum of kind of the device regulatory pathway, so preclinical testing through a clinical study and then all the way into a marketing application as well.

This is another voluntary program and the criteria that certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

And this is kind of an evolution of what -- of the Expedited Access Pathway. We had a final guidance for the Expedited Access Pathway, 21st Century Cures, and MDUFA IV, though, codified the Breakthrough Devices Program and kind of roll the EAP program along with peer review and the Innovation Pathway into the Breakthrough Devices Program. So we used to have a final guidance -- now we have a draft guidance -- for breakthrough devices, and so between the two of those, it will give you kind of an understanding of what we're going for here.

I mentioned, on the first slide, one aspect of breakthrough device eligibility, it's for devices subject to PMA, de novo, and 510(k) that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions and that also meet one of the four following criteria. So they either have breakthrough technology, there's no alternatives, they offer significant advantages over the alternatives, or making these devices available would be in the best interest of the patient. And the priority for this program is to make sure that we can come up with a tailored approach to expedite development and review of these devices given their significance while still maintaining the same statutory evidentiary standard that we need to support a particular

marketing decision.

And so there's kind of a few different aspects of how we're going to ensure that. One of them, and probably the most important, is the top bubble, which is really focusing on the fact that this is going to be an interactive and collaborative effort. There's going to be a high level of interaction between the FDA and the sponsor, senior management will get involved, and the goal is that throughout this process we're going to take kind of flexible and innovative approaches to answer specific questions that come up in order to make sure that we can generate the evidence that we need to feel comfortable with making the particular regulatory decision at hand.

And before we move on, this is a formal designation process. If you are seeking breakthrough designation, submit the request as a Q-Submission. Our goal is to interact with requests within 30 days to get additional information that we might need and to render a final decision within 60 calendar days.

And the last thing I'm going to talk a little bit about, real-world data and real-world evidence. We released a guidance document on this last summer, and the guidance document defines real-world data and real-world evidence as follows -- I'm not going to read these because they're a little wordy. The way that I like to think about this is that real-world evidence is derived from an analysis of information that's collected from routine clinical care. And the whole kind of focus of the guidance document, from my perspective, is the idea that just like with information that's collected from a traditional clinical study, care needs to be taken kind of at every step of the way, so from collection analysis to how that information is going to be used if you're going to try and use these kind of alternative clinical data sources.

Along with that, the guidance document highlights the idea of information needs to be fit for purpose. We will assess it for completeness, consistency, accuracy, and for

whether it contains all the information that we need to answer a particular regulatory question or concern at hand.

Within any benefit-risk framework, we want to make sure that the information that you provided is both relevant and reliable steps so that we can make an informed decision on the safety and effectiveness of the device, and the guidance document focuses quite a bit on the ideas of relevance and reliability as two aspects that are essentially data quality, and I'm going to highlight just a few of those points on the next few slides.

So relevance is defined as whether the data adequately addressed the applicable regulatory question or requirement, and the idea is that you're collecting information on the appropriate device in the right patient population with clinically meaningful endpoints collected at the right time using kind of tests and diagnoses that we can believe in. So it's really whether the information that you've had is going to be appropriate to answer the question.

And then along with that, data reliability has to do with the overall data quality and its aspects ranging from how the information was collected primarily, including whether there's appropriate patient permissions for collection access, and use the information, as well as the technical kind of aspects of how the information was collected. And then from a data assurance and quality control perspective, it's really focused on the entire process of that data collection all the way through curation analysis and use to make sure that we can have confidence in the evidence that's kind of generated from those analyses.

The guidance document goes into quite a bit of detail on these, it also includes examples, and there's a section on whether an IDE might be needed for certain data collection activities where you're looking at a real-world data source. There isn't quite enough time to go into those, and so I will leave you with the CDRH clinical evidence inbox. Please contact us with questions; our goal is to provide an interaction, answer questions.

Our commitment is to ensure that patients have access to safe and effective medical devices. We want to ensure that patients are protected, study subjects are protected, but that innovation is kind of -- we're not in the way of innovation. Thanks.

(Applause.)

MS. HOGAN: Thank you for that. Next up we have Bakul Patel. Bakul is the Associate Director of Digital Health, and together with Linda Ricci, these are the folks we go to when the companies we work with have any questions related to digital health, and everyone, of course, knows all the many initiatives the FDA has ongoing in this area.

MR. PATEL: Thank you. Thank you, Janice. Let me walk you through a few slides to just share what just got published last week, which is hot off the press, and give you sort of background information of how things are evolving really quickly in the space of digital health, not only in areas that we commonly -- and are associated, so health trackers and activity trackers. But as you see, the importance of this workshop is sort of highlighting the point that digital health is not just in the activity trackers, but it's actually in all devices we come across every day and as miniaturization happens.

But it really comes down to this slide about how do you sort of start looking at, you know, moving care from a clinical setting to the patients and where they live, understanding new aspects of patients as we sort of move forward, especially with the advent of the sensors and actuators that exist today and miniaturization of that. There also is opportunity to sort of learn more about how products that we regulated in the past and how patients behave with those products and what are the outcomes of that to enable us better care, again, focusing on, you know, in the case of implantables is one thing, but I think you can think about broadly as the topic of the entire effort of digital health is trying to get towards how can we prevent or identify things that can be prevented ahead of time so that can be better -- that can have us be better informed. It's all happening because of the computing

power that's becoming larger and larger as the day goes by, following Moore's Law, the sensors, as it gets smaller and smaller, the connectivity that is very ubiquitous. And we heard the panel on cybersecurity which talked a lot about with connectivity, you know; as Spiderman says, with connectivity, you have a lot more responsibility that you have to deal with, and you have to think about that as like what do you bring with that?

But also, there's opportunities to sort of how do you leverage that. And ultimately it's software that sort of brings it all together in terms of how we move forward. When you talk about software, I think about software in the medical device world in three different sort of realms: when software that by itself can become a medical device; and software that's in hardware medical device, we usually think about embedded software; and then lastly is the software that is used to make medical devices. And all of these things are important in terms of providing highest quality products and medical devices to the patients, and that's how I think about it.

But even so, on this journey of providing continuous clarity, and it's almost required in this space because things are evolving so quickly that we have to be on top of it, and it always has been risk based.

The two big things that we realized, since 2013 and '12, is we need to be focused on functionality, what does that thing do, because especially when you think about digital health products, digital health things that we may know of today as general purpose phones or sensors that we may not have -- not to imagine to be in the medical device space, but how does that sort of turn that into what does it do and what functionality does it achieve and does it achieve a medical device functionality or medical purpose functionality? So we've been focusing on that as opposed to focusing on the platform. It gives us that platform independence and allows technology and platforms to evolve at a much rapid pace without us sort of opining on how big or small this platform is or how big or small the

sensors are.

The second big thing that we have been focusing on is how do we keep it narrowly tailored and focused, because it's important as you think about different types of things evolving in the marketplace, medical products coming to the marketplace, not just medical products, but just general products used in health, how can we stay focused on what we do? How can we stay focused on the things that we regulate, have regulated, continue to be regulated? That's important to patients to give that confidence that we all seek as individuals, as a human being, as somebody and somebody who is involved in medical devices.

So this slide is actually a weighted defect that continues in the nature of the space where it requires continuous ongoing clarity for balancing innovation and patient safety. We've been on this journey since the publication of Mobile Medical Apps guidance -- final guidance in 2013. We actually started the journey in 2010 with a draft guidance and proposal that ended up in 2013 as a final guidance, but we continue to do this. In fact, just last week we published this guidance on multi-functionality that really talks about how do we take products that live in the space of -- surrounded by things that are not devices and surrounded by things that may be exempt or things that incorporate them into products -- functionality that may or may not be devices, that may not -- are exempt. So how do you think about that?

We had a similar journey on the international front because it's important in the space of digital health to be coordinated with our partners across the globe. And how do you take that and come up with a standard way of looking or a common understanding of what should software as a medical device, when it becomes a medical device, we should all think about? So we were on this journey for -- we started with, you know, a classic thing to do, settle on vocabulary, settle on a framework, understand what should software offer us

in terms of quality management systems, think about -- and ultimately, the last part was about clinical evaluation. It ties in really nicely with Joshua's talk about what should clinical evaluation look like for software that is a medical device.

So for folks in this room, it may not be very foreign because we're all used to doing clinical evaluations for different types of products that go into humans and get implanted, but when it comes to software, we're just so -- you know, not necessarily physical in nature, it was really hard for people to understand what that is.

And so we put up -- the international community put out this guidance on clinical evaluation and how do you sort of tackle that. It doesn't get into how to, but it does -- it talks about a common framework people can sort of goal; it aligns vocabulary in the world of in vitro diagnostics, which is very diagnostics-centric, to the medical device world that we all know today.

Bringing it all together, 21st Century Cures talks about qualifying our policies that we have had so far. We started the journey with the FDASIA health IT report where certain things are not medical devices. We knew that; we had not codified it. The law now codifies into administrative functionality is no longer a medical device. It was never -- but it's now very, very black and white, written in the law. We had a policy on general wellness, it was also codified, and so on. I won't read all of the slide, but it really talks about five big things.

And the last important or the last two important things I'll talk about is on this -- on what Congress did was codified medical device data systems; things that transmit things that are stored inside and display medical device data is not a medical device anymore. And that's one of the things that we had to now go forward and implement that. And the last big piece which we are working on right now, you guys all saw the draft guidance on it published last -- on clinical digital decision support, it's all the software that takes information from everywhere that you can imagine or any information that you can imagine

and provides support to clinicians. Congress basically said if it's transparent enough, and I'll probably not remember all the thing, but if a clinician or a healthcare provider can independently review the basis of their recommendation and not rely on it 100% to make the choice of diagnosing and treating, that would not be a device. So our proposal in the draft guidance was about to sort of -- was to clarify that. We have received a bunch of comments, and we'll be working on finalizing that in the next few months to take that to finalization so we can actually implement the law that was given to us.

I talked about 21st Century Cures where they also, along with that, I think we -- as MDUFA happened last year, in the commitment letter on the user fee negotiation, we all -- there was a request and sort of an agreement between the Agency and industry to explore a new streamlined pathway for software and include strengthening our bench in terms of our skills, our expertise. When I say skill strengthening, it doesn't mean that we don't have expertise, but we -- asked about not only bringing in the scientific nature but the business and the technology and sort of the understanding of how products are delivered in the marketplace as things sort of go forward in digital health. And we've been working through that.

I just talked through a bunch a guidances, and the 2018 check mark was the thing I just added from last week that we just published. However, for MDDS, Medical Device Data Systems, rule they are working towards withdrawing and amending those regulations that are no longer devices anymore, so that's going to be happening again coming up this year. That was our plan that we put out late last year.

This is kind of what we're trying to supplement our bench strength with. As, again, as I was saying earlier, there's a lot of needs and, you know, the cybersecurity panel talked about there's only 12 of those cybersecurity experts. We want 1 of those 12 so we can also have expertise in the Center. In fact, Beau Woods, who was on the panel, is actually on

the in-residence team that I have that's been helping us to think through some of the challenges along with Seth and Linda and others.

I won't read through all of this. The next biggest topic that I want to remind is artificial intelligence. I'm sure everybody's heard about it and talked about it, and everybody in this room probably is planning on using it in some way or form. And I'm sure people are thinking about how do you make that -- what's our role going to be, and we are working through that. But recently we announced this clearance that uses artificial intelligence, actually machine learning, to detect diabetic retinopathy.

But, really, it comes down to the fundamental scientific questions we always ask, you know, what's the verification? Is the algorithm correct? Has it been tested and validated? And, really, can it be generalizable before the population that it's been trained for and to the population that's it's going to be used for? And then how can you explain? That's the last part. There's a lot of things in here that's not uncommon, but it's also -- at the same time, it is challenging in the space of machine learning because it's not one algorithm, it's not one fixed algorithm, although some of the machine learning today is very much fixed and it doesn't evolve over time or continuously evolve over time.

What we're trying to see is how can we figure out a way where the data -- the rigor that needs to go into training can be equated to the quality systems that we would expect people to do in terms of the processes, and then how do you rely on postmarket to know how the algorithm and the machine learning system actually is performing? So we are looking at how we can explore that in the world of software, and this is just one type of software as we are going to move forward. The challenge does not end there. If you think about how we are looking at software, the timelines that exist for the development of software is drastically different than medical devices itself. The risks that we know, looking at it, physical product is different than when you can just say it's about software where

somebody has to sit down and describe what it looks like, so that's why in the case of artificial intelligence, interpretability becomes really important.

Again, in the world of software, I think pretty much there's a goal in the software community to have everybody program and make it so easy that anybody in the world can program, and you can see some of that happening already in the mobile apps world, and the question is if those all became medical devices and things that we would want to make sure that there's assurances, how do you start taking into account?

So I think this is a scenario where, you know, we've been trying to map our processes today in the world of software to what we know of today. But I think, eventually, and maybe it's not eventually but it's now in front of us, we have come to the realization that you can't keep on doing what we have been doing. I think we need a different way of looking at it, and how do you manage that, and how do you take that big square peg which is not in proportion to any round hole that we ever could imagine today?

So we're looking to create a system where we can take that further and address some of the challenges as we see. I hinted upon this as the current hardware devices. We understand some of the fixed algorithms and even machine learning fixed algorithms, we understand how to think about that, and then, you know, when you go into deep learning and continuous learning, I think there are some unique challenges that come across.

That leads us to what we've been sort of working on for the last almost 7 months or so since last July, is looking at an organization, thinking about how can we trust an organization with excellence, that's committed to the quality and excellence that we think is important, and then how can we give that trusted organization with the credit that it deserves so we drive the companies towards excellence as opposed to just meeting the bar that has been set?

And this is the vision of the program. Essentially, it's looking at the risk of the

product, which you already know how to think about, looking at the excellence of an organization, and then determining which products can go straight to market and which market -- which products would need a streamlined review.

And, again, leveraging, bringing it all together with information. I called it real-world performance, which basically means three things for me, is product performance, organizational performance -- actually, product performance, clinical performance, and user performance. How does a product do when it's in the marketplace from those three perspectives? It adds on to Joshua's comments about real-world data, so it is about that data but in a formatted -- or analyzed in those three things.

We put up five principles and these five principles -- I'm speaking really fast because I'm over my time, so pardon me for that. These five principles are something, if you look at all our regulations, it has been -- it has been sort of the bedrock of what we care about. We have taken those five principles, and said if an organization can show excellence in those five principles, we want to give credit back to folks, and how can we sort of take that and give that credit back and drive that excellence and look for that excellence in their organization.

We are working through all of these. We have divided -- or what we recently published last week was we have divided the work that needs to be happening in the space, in these four groups, four work streams. I won't read them all, but you can see it. It's really about how do you take the program from now until the end of the year, which is what we're trying to get to. We are committed to publish a Version 1.0, where typical in the software world to do 1.0 first, and that's what we plan to do by the end of this year, iterating again sometime next year and then a Version 2.0 by the end of next year. If folks in the room are from product development, you can recognize what we are doing; we are following an 18-month cycle, if not probably faster, and to do it in a regulatory circumstance is probably

challenging, so that's why I've been running back -- in and out.

So thank you for your time, but I would ask you to keep engaged on this topic, give us your feedback because it's only going to work with your input. So I appreciate your time and staying engaged. Thank you.

(Applause.)

MS. HOGAN: Thank you for that. Last up, we have Colin O'Neill, who, with Michael, organized the workshop. Colin is an expert in orthopedic biomechanics and mechanical testing, works on both premarket and postmarket issues related to orthopedic devices.

MR. O'NEILL: Thank you, Janice. So last talk of the day. I hope everybody has some reserve energy and caffeine left in their bodies. I'm going to attempt to cover some concepts and consideration that the FDA would like to encourage discussion on as it relates to the evaluation of SMART devices, and a lot of these topics have been covered in previous sessions, particularly the engineering and the clinical session, so hopefully I'll just tee it up again for additional discussion.

So we'll go over existing types of verification and validation activities that are currently established for orthopedic devices and move on to risk-based concepts and considerations that may be important for sensor devices. We will then go over a theoretical example to illustrate these risk-based concepts and encourage discussion regarding appropriate mitigation activities.

It's important to note that this presentation is not communicating new FDA guidance. We intend to introduce concepts for discussion that may apply to these technologies.

So when evaluating any type of orthopedic implant, there are types of preclinical activities that should be considered for appropriate evaluation. Mechanical testing can include evaluation of a device's strength, wear, and failure behavior. Applicable FDA

guidance and consensus standards should be referenced, and for sensor technology, it may be needed to be evaluated for its effect on the mechanical strength of the implant and its ability to withstand physical demands in the in vivo environment to sufficiently operate.

Biocompatibility testing evaluates the ability of a complete device to be biologically compatible. Applicable FDA guidance and consensus standards should be referenced. For sensor technology, new sensor materials and manufacturing processes may have an effect on biocompatibility and may need to be evaluated. Another consideration may be that an implanted sensor needs to be hermetically sealed, and durability testing of that seal may need to be a part of the evaluation.

FDA has issued many guidances on the requirements of software, and for sensor technologies, the complementary software may need to be evaluated based on its level of concern. There's major, moderate, and minor levels of concern. A major level of concern is when a failure of the software can directly or indirectly result in death or serious injury of a patient or an operator. Moderate level of concern is when a failure or latent flaw could directly or indirectly result in a minor injury to the patient or operator. And a minor level of concern is when the failure -- a failure or latent design flaw are unlikely to cause any injury to the patient or the operator.

EMC testing evaluates the risks associated with electromagnetic malfunction or degradation. Applicable FDA guidance and consensus standards should be referenced. For sensor technology it may be -- it may need to be evaluated for confirmation that it does not emit levels of EM energy that cause electromagnetic interference in other devices in the vicinity, like towel dispensers.

Usability testing evaluates the device if the device can be operated in a safe and effective manner by minimizing potential use errors and resulting harm.

User interfaces should be designed such that errors, use errors that occur during the

use of the device that could cause harm or degradate medical treatment are either eliminated or reduced to the extent possible. Again, applicable FDA guidances exist, and consensus standards should be referenced.

And labeling: Section 201(m) of the FD&C Act defines labeling as all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers or accompanying such article at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce. For sensor technology, labeling may include instructions on the interpretation of the sensor data output.

Additional validation may be necessary for sensor devices that provide patient data depending on the capability and intended use of your device, for example, passive monitoring, diagnostic or active closed-loop treatment. Appropriate analytical evaluation may be important to assess. For example, repeatability and reproducibility may be important evaluations to conduct.

So here's an example that actually Dr. Allen referenced in his talk. Some of the analytical evaluation provided for this heart failure monitoring system, the CardioMEMS HF System, which is a permanently implantable pressure measurement system designed to provide PA pressures, including systolic, diastolic, and mean PA pressures. These measurements are used to guide treatment of congestive heart failure, and some of this sensor testing, analytical testing, included accuracy, simulated use, sensitivity, etc.

And please note, again, this does not -- providing this example does not imply FDA endorsement.

One of the main potential considerations for sensor devices are how the output data are interpreted. The capabilities of this technology and associated intended use and labeling determine how the data are interpreted, which leads us to some questions. What type of data are being produced? And we visited a lot of different types of data that can be

generated from these technologies in earlier sessions. Also, how are the data being interpreted and utilized, and how does the interpretation drive treatment and ultimately affect risk? We consider these to be potentially important questions for the technology, and I'd encourage discussion after this talk during the panel session about these questions. And many of these concepts and lessons learned are being borrowed from other device areas so they may look familiar to you.

So diving a little deeper into these questions, what affects interpretation, application, and utilization of the sensor output data? Well, the validity of clinical association between the sensor output and targeted indications and patient condition may also be important. Whether the clinical association is well understood by the intended user, established and publicly available, for example, clinical practice guidelines from associations or published literature, or is it a novel clinical association, and this may be an important distinction.

We can ask ourselves benefit-risk questions such as can new risks be introduced to the treatment algorithm if the end user doesn't have reference to what the data means? And it's fair to say that, you know, if a sensor output data has a known and accepted meaning, that the risks of providing that information could be lower.

So the type of information provided and its associated and intended interpretation can (1) just be extra adjunctive information, meaning it can be used in conjunction but not required for the medical assessment of the patient; (2) replace and establish a portion of the treatment algorithm that's necessary for the medical assessment of the patient; or (3) create a new assessment for a new treatment algorithm, which some of these technologies will be able to generate data that we've never seen before and they may create new treatment algorithms.

The levels of risk associated with these intended uses may vary, meaning the level of

risk with adjunctive information may be different than replacing currently accepted treatment algorithms.

And, also, the patient condition for the targeted situation may also be important in establishing the level of benefits and risk as well. For example, in a recovering patient, infection may be more concerning than recording a step count, although in Dr. Bini's talk, the step count may be a very important evaluation.

So solely to illustrate the concepts introduced in this workshop, we came up with an example with a completely theoretical application, although it's been presented multiple times already. This is an example we found in the published literature, and you may be aware of this technology, and please note that the focus of this example is to only highlight the clinical concepts that influence benefits and risks. These examples and their associated applications have many important considerations, details, and caveats that we will not be covering.

So the concepts of measuring strain on fixation devices is not novel. Specifically, the correlation between strain and fracture healing has been studied for decades. The following example illustrates how the level of risks and benefits may vary with the type of information intended and intended interpretation with the SMART device. And, again, this is not meant to be an exhaustive example, just a thought exercise.

So here's a graph of a strain over time from data that's collected by the theoretical sensor, and here's what the doctor will see as the patient is tracked to post-op. The manufacturer purposely does not include strain numbers or criteria for interpretation or reference values in the labeling. So think about how the output information in this example relates to its influence on treatment algorithm. Is the association well understood by the intended user, established and publicly available, or is it a novel clinical association? And think about the appropriate labeling and instructions to define this type of use.

And then we move on to the evolution of that first example, and here's the same graph of strain over time from data that's collected by the sensor, and here's what the doctor will see as the patient is tracked postoperatively. And in this case the manufacturer has determined that certain data such as patient demographics, fracture classification, etc. correlates to a particular trend line on the strain versus time graph, and now the patient's strain data is compared to the expected trend line and the doctor can look for abnormalities. In this example, is the correlation between these variables in the fracture trend line well known and/or well understood? What are the adequate instructions in order to help the surgeon determine what level of deviation requires action?

Moving further, here again, here's a graph of strain over time. Here's what the doctor will see as the patient is tracked post-op. In this case the manufacturer has determined that certain strain characteristics correlate to a diagnosis of nonunion. Now the doctor has the ability to replace existing diagnostic tools in their current treatment algorithm. In this example, is the diagnosis of nonunion based on the strain reading at the fracture site well known and/or well understood? And what would the appropriate labeling look like for the diagnostic capabilities in this scenario?

Moving further, here's the same graph and here's the doctor, what the doctor will see, and in this case the manufacturer has determined that certain strain characteristics correlate to a diagnosis of nonunion. Now, the device actually has a closed-loop active bone growth stimulator incorporated into the implant. It's programmed to deliver therapy based on the diagnoses from the sensor. The doctor now has the ability to replace existing diagnostic tools and therapies in their current treatment algorithm. So in this example, is the point at which the patient would benefit from stimulation based on the strain reading well known and/or well understood? What would the appropriate labeling look like for the therapeutic capabilities in this scenario? For example, how long would the simulator run

based on a certain strain output? For each of these examples, think about how the output information benefits the patient and the end user.

So SMART sensor technology in the orthopedic space is new to the Agency, and as part of a collaborative effort to help develop a streamlined regulatory process, we hope that you consider the following questions for discussion: What is the clinical meaning of the sensor's output, and how does it influence the benefits and risks? How does providing adjunctive information in the clinical treatment algorithm versus replacing part of the treatment algorithm change the benefit-risk profile? Consider how the benefit-risk evaluation changes as the capability of the technology starts with monitoring and involves the diagnostics and active treatment. And how does increasing influence of the sensor output data on clinical decision making affect benefit-risk and therefore the level of risk mitigation activities necessary?

And a few more points to consider for discussion: How information is communicated to end users and patients is important, and therefore, labeling is important. The communicated intended use of a sensor's output data should undergo benefit-risk analyses and, if necessary, appropriate risk mitigation activities. Patient labeling should be considered to appropriately communicate the benefits and risks of the product to the patient. And as technologies evolve and the capabilities of them evolve and new output measures are validated, changes to device labeling should be considered to communicate appropriate updated information to users and patients.

So if you have any specific questions about a certain device, we might be limited to giving you feedback in this format, so we encourage submittal of Q-Submissions or pre-submission to get detailed feedback about specific devices and questions related to those devices. Yeah, and that's it. Thank you.

(Applause.)

DR. SOVES: All right. Thank you, Colin and thanks to all of our speakers today. With that, I will open up the floor if there are any questions from the audience at this point. Regulatory considerations. All right.

DR. YATES: You can't have a panel without questions. And I'd like to just open up by thanking the FDA and specifically the organizers of today for a fantastic afternoon and morning, and I really appreciate it.

(Applause.)

DR. YATES: I had a couple of questions for Josh, if he doesn't mind, and the first one is the Clinical Cure Act or the Cure Act from Congress is very recent. When I pick up my journal, every one of the companies says that their technology is breakthrough, at least when they advertise to me. How many breakthrough technologies have gone that route so far, or is there an example that you can give without violating confidentiality?

DR. CHETTA: So as you mentioned, because it's relatively new, I think we have a few examples of -- we are currently evaluating applications for designation. I'm not sure if we have any publicly available.

MS. HOGAN: I'm only allowed to say when a client has announced it themselves, but the example that Kul mentioned, IDX, they disclosed that they had expedited/breakthrough designation.

DR. YATES: So there hasn't been a rush to the door for that so far. I mean, it strikes me as being an expedited way of getting something -- did you feel that way, that it's going to be somehow used to expedite processes that would otherwise go through standard evaluation?

DR. CHETTA: I mean, that's our hope. Our hope is that it will -- I mean, by working collaboratively with companies, taking kind of a creative approach to addressing the regulatory needs, our hope is that, yeah, we can get technologies to patients faster.

DR. YATES: And then my second question is kind of getting into the weeds and -- but it's about evidence-based medicine, so I'm interested in that. You mentioned real-world data, but give me an example of what real-world data is. Is that like a meta-analysis of postmarketing reports, is that registry data, and if that is the case, what's the transformation methodology used to go from the data to the evidence? In other words, do you use grade technique or one of the other types of evidence processes?

DR. CHETTA: So real-world data can encompass a number of different data sources. You mentioned registries. That's one that is a source of information that we've seen used successfully, particularly in the cardiovascular device space in the last few years. We have seen companies partner with particular hospital systems to use their EHR systems to extract information directly from that. It could be, you know, kind of similar to like an observational kind of approach. There was another question that you asked and I --

DR. YATES: The other question was when you have the data, let's say it's a set of 30 papers, postmarketing, there are methodologies for determining evidence and level of evidence or recommendations. Any particular methodology?

DR. CHETTA: So the guidance document is agnostic with respect to methodologies. The focus is -- it is descriptive in terms of the types of considerations that we think are going to be important for understanding the overall quality of the information. So what we're looking for is adequate kind of detail that we can understand how the information, you know, the data were collected initially, how they were analyzed and kind of ultimately how they're used. But we want to get kind of a comprehensive view of everything that went into that. So we're not tied to any particular methodology, no.

DR. YATES: Okay.

MS. HOGAN: Just one comment. I want to give the FDA a big thumbs up for two things they've done related to your question. So you asked about breakthrough

designation. I think this is dated, but I think in 2017 the FDA published that they had granted, at that time, about 17 requests for old expedited designation, just to give you some sense of scale. And the IDX submission, which, you know, not everyone will be like this, but as we talk about really innovative things like SMART orthopedic implants, the company disclosed itself, it was a multi-thousand page submission with a multi-hundred patient clinical study, first application of artificial intelligence to diabetic retinopathy, the FDA cleared it in exactly 90 days. So I think that just shows you like the commitment to really working on some of these things.

And on your question about methodology, the FDA's been super helpful in helping companies figure out how to use meta-analyses and use different epidemiological methods to get new claims or work on submissions, and I think that's an area where the FDA, at least for my clients, has so much more epidemiological knowledge and expertise, they've been super helpful.

MR. WALE: Baxter Wale (ph.) with Aureus Medical. Dr. Chetta, another question for you. I saw in the last, I believe, a week, I believe it was Novartis got approval for using an app to prospectively gather data in looking at trials in ophthalmology. I'm curious if you see similar approaches to these SMART devices and/or patient data apps for getting more traditional approvals --

DR. CHETTA: So we are excited about the prospect of using medical device apps, kind of reaching out to patients. We've seen companies experiment with using those apps to identify patients that might want to be enrolled in a trial. The inclusion of things like patient-reported outcomes that could be, you know, those types of data that could be collected through an app, we're also very interested in. So we see a future for it, and we're open to it.

MR. VARRICCHIONE: Hi. Tom Varricchione, Ximedica. I have a question for

Mr. Patel. The software precertification pilot program was limited to a small number of software developers. I'm wondering if the Agency feels like they're getting adequate representation of the diversity of software development that takes place in the medical device industry, and if not, are there plans to do something to expand the kinds and amount of input?

MR. PATEL: Just two things. I think the nine participants were chosen to just get the representation that we needed to start with. In fact, our goal has been always to get input from everybody as we move forward. The reason to publish the plans and the working model last week was exactly to do that, and my message has been stay engaged. So it's just not the nine that we think are going to be helpful, but the entire program will depend on input with anybody in the space who can bring that to the table.

Going forward, I think when I say after -- 1.0, we will be opening it up for other tests or participants testing the model as we sort of bring it on next year, and we'll have a process to announce that and get names to participate in the next phase of that iteration that we probably go forward with.

So, yes, it's based on not coming out typically as FDA usually does, is we put out a draft and here's a final. It's actually very iterative. We can see, even as we laid the roadmap out, it was very -- it should be very evident that this -- that model that we put out is just the first line, an initial model, and we'll be updating that throughout the year until we get to the end of the year. So an input and every input is going to be welcome for us, so please, please, again, I can emphasize, engage.

MR. DURGAN: Hi. Bob Durgan, Johnson & Johnson. I, too, would like to thank the Agency and congratulate all of you for hosting what I think has been a very successful workshop. I know it's been enlightening to me, and I'm sure all of us have benefitted from the robust discussion today.

I also have a question for you, Bakul. You noted during your talk that the 21st Century Cures Act, you know, had a very interesting caveat with respect to when clinical decision support software is not a medical device. So I'm just wondering whether there have been any published examples of a determination of when the software did provide sufficient, reliable, independent ability of the clinician to determine whether or not the Act was providing a recommendation that could be followed.

MR. PATEL: So you hit up on something that is really complex and was also very interesting, and that's what the law has provided. There's a four-part test in the draft guidance that we proposed, and we got a bunch of input on proposing anywhere from, you know, being very open about the algorithm to knowing -- citing a bunch of papers to everything else under the sun.

I think the question is going to be really what does that transparency for people -- and what does that look for? We haven't settled on anything yet, and that's what we're working through. But that's exactly the point, is Congress has said, you know, determining two factors like users can understand the basis of a recommendation, and that can mean many things, and also not to rely on and that gets complicated really fast as, you know, what is the basis of the recommendation and then what does reliance mean? And I think, as a result of that, it really translates to how transparent and understandable the recommendation from the software is and how is it well understood or not. So I think as we sort of work through those things, we'll be working through probably, you know, folks like you to figure out how do we sort of make that clear.

MR. DURGAN: And I was just trying to verify that I hadn't missed something and there was actually a publicly available example of a determination one way or the other.

MR. PATEL: No.

MR. DURGAN: Thank you.

MS. HOGAN: One more question for the panel that I got from a client, so I'm going to pick up on Bakul's theme of with great power comes great responsibility. So with all this information, there might come some responsibility too. So if there's a tremendous influx of new information either to clinicians, patients, payers, or in some de-identified way to manufacturers, I think companies are curious about what does this mean for them. So, for example, if you're getting a de-identified voluminous stream of data that shows that 10% of your implants are rocking, is that a complaint? Is that reportable? How will the FDA, just at a high level, go through the process of figuring out how this kind of information fits into your regulatory framework, rule making, guidance?

MR. OWENS: So I'll take the first stab at it and make sure that the rest of my colleagues up here have a chance. So I had an interesting conversation with one of our medical officers a couple days ago about this very question, and he kind of likened it to the existing liabilities they have right now with, say, for example, like a mammogram screening and the liability you have if you don't -- you know, you have a positive reading and somehow it falls through the cracks and you don't call the patient back. So I think that I'd love to have any of the clinicians come up and talk about their thoughts on that kind of liability with this volume of data. But in regards to -- from a regulatory standpoint, I think that the volume of data, to me, seems like more of a resource issue, but I'd love to have anybody else kind of give their thoughts on, you know, what our role is in that question.

MR. PATEL: Maybe I can comment on that. So where the Center is going with real-world data collection and awareness is the proactiveness part is, I think, were we expecting folks to do any -- and you can see this is the case of quality, case for quality in other areas as well, is this is more about -- so can we have -- is the availability of information and taking action, this is exactly what quality management systems talk about, okay, being corrective and preventive. And then when you talk about preventive, it's being proactive. So I think

that's the part and, you know, what Michael talked about is, you know, I would rather think about the fact that something fell between the cracks as a sort of last thing.

But I think the advent and availability of data should be used as an opportunity to sort of, you know, head off anything that could potentially happen and rather than, you know, it's the same thing that -- you know, we talk about signals to noise ratios, like is it really a signal, and do you have processes and methodologies to sort of identify the signal and make sure it is actually -- can that be used as a leading indicator?

And that's really where we're heading with this entire effort across the Center from -- not just from real-world data but also, you know, from a software perspective, from connectivity perspective and, you know, cyber. You can see the same themes sort of appear that it's not okay to just sit around and wait for something to show up; it's the proactiveness that's necessary to sort of be -- you know, in the cyber world you can talk about threats that may emerge in different areas that can be sort of added to. So that's really the theme that we are looking for, and manufacturers.

DR. YATES: You asked for a clinician. Bottom line is, is that that feedback loop of that positive mammogram reading getting to the patient and it being actionable items, that something happens, is part of what we're looking at in terms of our next generation of imaging and reporting, so that the feedback loops are invincible, you know, that you have to be able to do it.

I mean, the Veterans Administration in Portland, Oregon, had an incredible process where if the radiologists saw a nodule on a chest x-ray, that patient was automatically enrolled in -- to see the pulmonologist, had a biopsy scheduled, everything, just off of that one finding, the CT scan, and go to work. You know, it can be done and it doesn't -- and in big numbers, you know, shame on an implant company if they have a 10% failure rate and they can't read their own data to see that 10% are failing. If we miss 1 out of 1,000

mammograms and somebody ends up with metastatic breast cancer because somebody didn't report it to the patient and act on it, that's a huge loss; I mean, that's not Six Sigma. And I would hope that industry doesn't send the FDA data in such a raw form that they don't know what's in it. I mean, that would be buyer beware; I mean it's caveat emptor in terms of using the FDA as your -- trying to help you. Be sure what you send. It's a high standard and they should be held to the same high standard.

MR. RAMSEY: I was just going to chime in a little bit from a postmarket perspective. I mean, I think that this -- the question you asked about how it gets reported or not reported, I mean, to me if you read the 820 regulations, you know, you're supposed to analyze all sources of quality data, so this would be a source of quality data that if you had access to it and I think the general expectation, I would think, does it change? I think now there's a new tool, and we acknowledge that there might be different ways of analyzing it, but the expectation would be, at a minimum, to, you know, incorporate that input into your quality system and then use that to sort of drive any future kappas or, you know, recalls or labeling changes or things like that. So I would say that it's -- not that there would necessarily be a paradigm shift; it's just now there would be another input to your quality system.

DR. BAUMANN: We have an online question if the panel would care to hear it. How would the risk-benefit analysis change if a company wishes to utilize a SMART device to substantiate device claims?

MR. OWENS: They said the C word, Raquel.

(Laughter.)

MR. OWENS: Colin, do you want to take this?

MR. O'NEILL: I think the sensor capabilities and evolving indications and such, they're going to potentially alter the benefit-risk profile, and it's not really determined

when sort of risk mitigation activities are going to need to -- that information is going to need to be provided to the FDA as these things evolve, potentially when they're on the market. But, yeah, benefit-risk is going to be a huge consideration with balancing the amount of information you need to provide with the evolving capabilities.

MR. OWENS: I have a question I'd like to pose to industry, if they want to join the conversation. I was doing a quick search of the CardioMEMS just to look at what type of adverse events get reported for that type of technology, and I saw quite a few of them that were about, you know, having problems deploying the device, the receiver sparking. There was one about inability to calibrate the curve and having to abandon the procedure.

What I'm interested to see is how you would approach, from a complaint and/or reporting requirement, if there was just a misinterpretation of the visual graph. Do you see that as a response? If a doctor says this looked like it was going up enough to treat, you know, the slope of this graph was enough to treat the patient and that was incorrect, do you -- what responsibility do you as the industry have, and do you see that as a reportable issue, and how would you report that?

Does anybody want to take a stab at that? Stacy. No? I mean, I would -- so my response would be, I would hope that it would be, I think that that would be crucial for us to understand how these devices are being used and what the issues are with them and to understand what the kind of backup response can be and really had a kind of full circle, bring that into our review of improving these devices down the road. What do you think about that, Janice?

MS. HOGAN: Well, more and more of our clients have to think about what they have to do here, what they have to do in Europe, what they have to do everywhere. So if anywhere in the world you have an affirmative obligation every 2 years to update your risk analysis, you're basically going to be doing this anyway, right? And here, even though you

may not have to submit that to FDA, it's still part of your quality system obligation, so I agree with what was said before. So there's the premarket risk-benefit, but then there's also your postmarket obligation to keep continuously updating your risk analysis.

UNIDENTIFIED SPEAKER: I don't have direct responsibility for that sort of thing, but I would say from my days in product development that we would look at that as a human factors engineering issue. We would try to understand why did the doctor misinterpret it, and what could we do to sort of help that in the future, you know, icon changes, color size and things like that and then report it as such.

I have a question, though, about the real-world data to real-world evidence that you were talking about earlier. This is a really basic question, and I'm sorry if it's stupid, but if you analyze a lot of real-world data on, say, a product that was used off label and then you could create or you analyze, in a very pure way, the evidence that says it was advantageous to use, does that become evidence that you can use supporting a label claim or a new indication?

DR. CHETTA: It could, yeah. So one of the aspects that the guidance document kind of tried -- one of the -- there we go. So one of the things that the guidance document kind of tried to address, and that we're kind of dancing around, is that the Agency doesn't regulate the practice of medicine, and we recognize that physicians are using legally marketed devices in ways that may be kind of different from their labeled use and that's -- you know, if that's in the best interest of the patient, you know, a healthcare practitioner-patient relationship, that's perfectly legal, and we hope that patients are getting the best care that they can. The doctors are using these devices in ways that they think are best and if -- you know, I mean that's kind of how clinical practice changes, kind of over time, right, as people recognize that this is a good way to do things and then kind of clinical practice shifts. This is a way for hopefully the Agency to recognize that that could be a valuable

source of information, and if the information that's collected is, you know, high quality and we can feel that it kind of meets the level of -- the statutory level of valid scientific evidence, then that absolutely would be appropriate for supporting a, you know, marketing application.

UNIDENTIFIED SPEAKER: Hi. I have, I guess, less of a question and more of an observation, but if people have a response to it, I'd like to hear it. One of the things I've heard throughout today is really the ability for these devices to be interoperable is crucial. So you have the example earlier of your fitness tracker and your scale and MyFitnessPal not communicating with each other.

So, you know, I'm wondering if there is sort of an observation maybe from the panel or others about who is going to motivate that interoperability? So, you know, individual device companies may be operating within the sphere of what they're working on but not necessarily branching out across these technologies. So, you know, some thought about whose responsibility or who is going to be the driving force for that interoperability to become not a feature but a requirement of this medical device space.

MR. OWENS: I think that's a question that the industry should weigh in on, but I will say, you know, I was asking for a few talking points from one of our UDI experts, and she pointed out that the UDI program would be a good place to start in regards to interoperability and the ability of the devices to identify one another. But that's about all I know about the UDI.

MR. PATEL: There is actually a big push in the Center, not just recently, but there's been for a while, on pushing interoperability in the right direction, and it's not just about, you know, in this particular space, but you can think about it from a large effort and Michael's standing there, he's probably at it, too, from a lab perspective, also. There is actually a guidance that actually allows people and people who are thinking about getting

into connecting and collecting data and sharing data from their products to other products, should look at that interoperability guidance that we published a couple years ago. It talks about two fundamental things, like if you use standard-based interoperable standards to use in your products to share data, it is well accepted, and FDA will accept some of those standard-based testing that's highlighted; two, if you use a proprietary based protocol to share data, but at the end of the day be very clear and transparent about how you're using -- how people should use or other machines should you use, that data use that you're transmitting or sharing is something also that we would be very, very happy to encourage and make it easy in the reprocess as well, the goal being we want people to share data in an interoperable way, not forgetting cybersecurity at the same time.

Also, I think about interoperability and cybersecurity as the yin and the yang, we need both to sort of advance going forward. We want users and machines who are going to use this data, to use it safely and effectively and that is the message for interoperability.

And we've been working with many stakeholders; in fact, we are continuously evaluating standards that come out in the space, not necessarily only for a medical device, from IEEE and from the software engineering space that really, really relies on interoperability and making sure that the products actually do talk and talk in a way that is understandable, secure, and ultimately provides safer and smarter solutions going forward.

And that's what we've been doing leaning forward. I think there's a lot of interest, not only at the Agency but also in the device community. And I think there's going to be a push and a pull from a lot of directions that needs to happen to providers, the purchasers, the hospital units, should be looking for that and asking for that, just like we are allowing and enabling and creating an environment for folks to sort of take that and take it to the next level of being interoperable and secure at the same time.

MR. WATERS: So just to back that up. There are a lot of ongoing efforts currently to

get engaged in different interoperability areas regardless of what area you're going to. This is not just within CDRH or, you know, just in the ortho spot, but this is across diagnostics, it's across FDA as a whole, and there's many inter-agency multi-stakeholder efforts, and if you want to get engaged, you can reach out to us and we will help you get in contact so we can make sure that your voice is represented. It's really important. We think the semantic interoperability and interoperability of devices is absolutely critical for the future and helping enable new technology, so yeah, a great question.

MR. PATEL: Yeah. And just to go back to support Michael, I think reach out to -- you can reach out to me directly if you want to be engaged in some of those activities, reach out to Michael. We not only coordinate within Agency but also across HHS and other parts to sort of look at how do we bring this interoperability together because it's actually an important aspect and important strategic priority for us.

DR. CHETTA: Can I return very quickly to the question about off-label use? I should have highlighted that if you want to do research on off-label use of a device, that may need an IDE, and we would strongly recommend that you come in and speak to us. That's it.

(Laughter.)

MR. PATEL: Can I just add to that question about, you know, what happens when you find information of your product and then now suddenly you find that, oh, it can be either enhanced in the next submission or we have to do something else with it. I can just give you an example of a company, I will not name them, but they did a similar study. It was a nonsignificant risk study, and eventually they found out that they were better off, to avoid any adverse events, to put a contraindication on the product, and they did that. And, actually, that enhanced their product so much, it was phenomenal to see that.

So I think it goes both ways, right, it goes both ways in terms of, you know, enhancing your key claims in terms of how your product can be used, but you can also think

about this as a risk mitigation factor that removes some of the burden from you in terms of, you know, managing, being proactive in the essence of being, you know, corrective and preventive going forward, so think about it from both angles.

MS. HOGAN: One other generic comment that we haven't really talked about much but we get a fair bit of questions from other clients about, so from what we know from other types of sensors outside of orthopedics, I think we've learned over the years that you really have to think about who's going to use the information and how. So, for example, if the doctor is receiving this information, we didn't talk at all today about if the doctor is receiving a big, new stream of information, how they get reimbursed for their time to review it, how often are they supposed to look at it, is that part of the procedure code, is there some other code for it, is it in a general telemedicine code? I know only enough about this to be dangerous, but in other areas that's been a big issue because you create this new work stream of having to look at the data and do something with it.

And another interesting one is maybe this information that you would get off of a SMART orthopedic implant was never intended for the patient, but does the patient have a right to their own information? In personalized medicine, that's been a hot topic. People now are used to getting a lot of information on their mobile devices about their own health and if somebody has an implanted sensor in their body, I think there's a lot to think about there about who's entitled to that information, how they have to be trained about it.

MR. OWENS: I would also add that plays a role in clinical studies on if the patient were to request to see their data and how that could influence the performance in the study and how it continues to go on.

I would add, to kind of -- to open up another discussion, if it's okay, the clinicians kind of touched on the clinical applicability of these and I kind of wanted to just discuss, from a regulatory standpoint, where clinical data plays a role in what we kind of mean by

that and breaking it down into the kind of buckets based on risk. And Colin and I have discussed this a few times and basically, you know, it's our definition of valid scientific evidence applies here and when we say clinical data, I just want everybody to know that we are open to being creative with this technology, understanding the benefits and trying to understand the risk. And some of these, you know, measures are available in literature or in clinical guidelines that can supplement the device and something that we'd be interested in discussing with you and hearing your thoughts on in regards to the continuing evolution of these devices.

MS. HOGAN: One thing we've talked about is whether we would see a lot of new longitudinal claims, like once you have all those implants with that information available, would people be racing with each other as they do in some other areas to say now we can make a 3-year claim, a 5-year claim, a 10-year claim, because it's always been so hard to retain people in longitudinal studies, but will this fundamentally change the availability of that kind of long-term data?

MR. OWENS: Which is always a hard thing to get for orthopedic studies.

Dr. Yates, I'd be interested to hear your impression on, you know, where -- what kind of evidence you would need to implement, say, something that's been studied in literature but not in vivo on an implant, but it's a metric that was -- you know, that is understood by you in literature and it's just confirmed that it can measure that in vivo versus going to the other spectrum of somebody's trying to provide you with a new measurement tool that is measuring some kind of new metric that isn't part of your normal care but could replace something it doesn't have, you know, a basis in, you know, your upbringing as a -- you know, your medical education.

DR. YATES: Well, part of the problem is, is that if it's a new data stream with a new metric, then it will not have been in our literature so there's nothing to correlate to. So it

would have to be almost -- whoever would present that to me would have to present preliminary data and would have to come to me with some sort of evidence for there being a connection between that data and an honest to goodness healthcare state that has importance to the patient.

You know, I work with the National Quality Forum for the Standing Surgical Committee, and we look at processes, and you're really talking about something that's measuring a sensor process or a surrogate for health, you know, it's some sort of set of data points that are being given by the sensor, when you look at processes, they have to have a much higher level of evidence in the literature or in equivalent literature to say that it can somehow be tied in to a healthcare state that's, again, of value to the patient. You know, we don't want to just measure things to measure things.

So I think it would have to be something that would be readily -- what's the best way to put it -- translated into something that I can use to better advise the patient on prognostics, better advise the patient on their utilization of a device, better advise them on what their new symptoms might be coming from, and that's going to be very hard unless somebody's got some preliminary data, as a clinician.

As a researcher, you know, it may be something that you develop on your own, but you're asking me if someone comes to me with that what's the pitch, you know, what's the sell, and right now, that's kind of a tough sell. We talked about this earlier, a bunch of us, that total hip replacements have a 95% success rate and the survivorship, barring, you know, surgeon error or dislocations or infections, we're talking survivorship now of 98% over 10 to 15 years because polyethylene is so much better. We can't even see wear anymore.

So some of the things that sensors may have been in evolution to capture over the last 10 years as people developed them, they may have already missed the boat in terms of

when we needed them. We really needed these sensors 15 years ago to measure for early loosening or for, you know, some sense of inflammation from polyethylene wear. So that's one where the sensors could have been better earlier.

I think ultimately the sensor technology in orthopedics is going to come, and this is really somewhat pie-in-the-sky, but industry has billions of dollars invested in it. When we make the next paradigm shift and we go from the punctuated equilibrium of hardware for the last 40 years and we go to biological resurfacing, biological treatments, when we are taking scaffolds and creating knees that have living tissue or put in hips that are actually, you know, designed and 3-D printed to go in and become a real hip again, I think that's where the sensors are going to become incredibly important because that's going to be a brave new world that we're going to need to have information from in terms of early failure and where things could be going wrong.

That's sort of science fiction, but that's the best answer I can give you right now. I think that the degree of information for, at least, major joint replacement hardware is going to be a little bit of a harder sell right now. I think that we missed that boat 10 years ago.

MR. OWENS: Yeah, that will be real interesting to see, as the patients become younger and the requirements on the device double, that these technologies can help, you know, still have a role in arthroplasty in the future as these younger patients are receiving arthroplasty and the expectation is 30 years possibly.

DR. YATES: And the materials testing for some of the polys are 30 years they're surviving, but that's in -- that's not in vivo. But would the technology we put in now, 30 years from now, (a) be functional and (b) be up to date with what we really know what's happening. In a 30-year scenario, a failure that we don't even know -- we didn't even know trunnionosis was something we had to worry about 5 years ago, and now we're chasing, you know, all sorts of different rules and algorithms with MRI and synovial fluid analysis and

cobalt and chromium levels to try to define what exactly trunnionosis is and that can be, you know, different on five -- from five different people on the same panel, you know, at one of our meetings.

So I'm not trying to discourage SMART technology in that particular format, but I think it ought to be looking at the -- you always -- you're looking ahead to the horizon, you know. I think Yogi Berra had said it's very hard to make predictions, especially about the future, so we'll see.

I have one question for Dr. Patel. This is like where a little knowledge is a dangerous thing, but you were talking about software in the -- at the level of machine learning and AI, and machine learning is -- it has been explained to me by very smart sons, has to do with some basic assumptions that have to be put in, and then it's the data that's put in that makes the machine or it leads to that. But especially with AI, do we run the risk that software that goes out into the real world diverges, that one device with one set of AI software eventually becomes just a little bit different than the device in, say, another robot that's helping with the surgery?

MR. PATEL: So I don't know if you're heading down this entire personalization of products that we're heading towards and maybe that's where you're heading to, where something trained and, you know, for a set of conditions or a set of patients and we know it's for a study and then it gets implanted or used by me and starts personalizing from my conditions, will be different than Josh's and then Michael. So I think that's already happening. It's called Nest. It could be in your house, where you buy something that is learned and preprogrammed, but then it learns when it's in your home to your patterns. I think that's where we're heading towards, but it's based on data that's really generated by you and by your physiology, by your condition. So I think that's where we're heading and that's exactly what machine learning is very powerful for, is to recognize patterns from

data. I don't know if that's where you're heading.

DR. YATES: Well, let me take it to robotics.

MR. PATEL: Yeah.

DR. YATES: Robotic-assisted surgery, for instance, which is a hot topic. And you know, we're using, you know, software from 10-15 years ago where it's set, you know, it's programmed. If somebody decides to put some AI into the robot and that robot happens to get matched up with a surgeon that doesn't know how to read the graphs, like what was brought up earlier, or doesn't -- or tells the robot to do something else and all of a sudden, you're got this big divergence, is there a possibility of the human/AI interaction leading to errors that we never --

MR. PATEL: So you're absolutely right. So you're talking about risks from just training, and yes, those are some real risks that can happen, and this is exactly what we're looking at and saying what can the rigor go into training those machine learning algorithms just so that we are not diverging away from what the intent -- real intention of that particular product is. And it's not something that is taken lightly by us, but it's also even the AI community is very aware about, you know, potential diverging away from where the original intention was.

So it is possible. In theory, it's possible, but there are always some checks and balances, and I think those checks and balances need to be there. Continued validation is another aspect that can be considered as well. Retraining. And there's many techniques in the world of energized MEMS that that's where AI is -- and stocks has actually been one of the biggest sort of breakthroughs where AI has been used a lot, and those kind of things will have to be maintained and those kind of rigor would have to be sort of put in place, especially to create a predictable field where actually AI can be beneficial to the data that we have.

DR. YATES: And I just want to draw a really quick distinction here. AI has a larger definition than adaptive learning. Adaptive learning is one area that you can go down and AI also has a lot of implications for things that are currently in place, so sorry, just a little geeky point that AI, with respect to like image analysis, for instance, is already in many, many places and already actively helping people.

MR. PATEL: So I just want to make one point on the previous question that Michael was asking about, you know, what if -- and I think he responded really well about if somebody brought you a pile of data, if it's not clinically associated or has some association to a clinical condition, it's hard to know. I think we're in an age where data and machine learning will associate, but in order to associate, you have to generate data and in order to generate data, you need to have sensors and in order to have sensors, you need to make sure the sensors actually are in a place that can actually give us meaningful data that can eventually get to the association that we look for.

You know, today that's the difference between using data to find association as opposed to using a bunch of trials and studies to find an association. There is the difference that this world is heading towards in the world of digital health. I mean, that's the encouragement we want to see, is like people collecting data and then getting to an association which can then be validated, that we may not have seen in the past.

I mean, the questions that Michael and you are pondering upon is the materials that we know of today could be predicted to be going down to the very basic science of -- could take us to a point where we can actually predict whether it will take 30 years or 40 years for that implant to last and that's something can be done with data and there's a lot of smart people working on this to predict and that's one thing that's good about AI and machine learning, is to use that technology to make those predictions. But it has to be validated for us to be seen to be predicted. So I think there's the -- there is sort of the area of machine

learning and digital health heading towards.

DR. YATES: Since I'm just sitting right in front of IBM's representative, the answer is I'll ask Watson or what's his name.

(Off microphone response.)

DR. YATES: Yeah, okay.

(Applause.)

DR. DMITRIEV: Well, ladies and gentlemen, I certainly pulled the short straw in trying to offer closing remarks after a 9½ hour marathon of the day that we had, but I think I would like to highlight a couple of points of importance that we covered throughout the day and definitely thank everyone who are still sitting at the panel and throughout the day.

We've covered a lot of ground, and we probably did not come up with answers to a number of questions that we raised. We started with laying the foundation, the basics for sensor technology, we talked a little bit about the specific applications. We raised clinical considerations, we talked about the type of information we should be collecting. We did address the cybersecurity concerns, or at least we talked about them, and certainly we raised the regulatory considerations for this technology. We spoke with two patient representatives.

So the question now is where do we go from here? And I think we look forward to your feedback. We encourage you to certainly take a look at our docket, which I will show in a few seconds, once again, so that you remember and maybe you could go back to the announcement and actually submit comments, submit feedback of the type of things that you would like to see down the road. Is there room for a subsequent meeting? If there is room for a subsequent meeting, what type of form should it take? Please tell us what you would like to hear and what you would like to have covered in a subsequent session if we are to convene one, but please don't raise bad questions such as what do I need to get to

get my technology approved? Eventually I think we will get there.

But in order to wrap this up and not be in the way of -- and not be the last thing standing between you and the afternoon sunshine in Maryland, I wanted to say thank you to the organizers, our CDMI folk, Dr. Jeffrey Lotz, Dr. Vijay Goel, Dr. Stefano Bini, and Aenor Sawyer; our representatives from industry, Hassan Serhan and Brian Schlossberg, who are part of CDMI, definitely the National Science Foundation, and also helped us organize the meeting.

And I wanted to highlight the contribution and hard work of my FDA colleagues: Andrew Baumann, who is sitting right next, to the right, as well as Colin O'Neill and Michael Owens, right in front of -- at the podium still; Shiril Sivan, also sitting next to Andy; and Susan Monahan, who is in the back but she was instrumental -- she's not here, she's actually at the front. She was the lady that was checking everybody in. But she also was instrumental in securing the venue and making sure that we got all of the approvals right. The management teams and all the support that we've gotten as part of organization of this workshop and certainly, all of our invited lecturers and panel moderators who have taken the time out of their busy schedules to spend the day with us and engage in the discussion of SMART technology in orthopedics. We are laying the foundation for something new, and I think it is exciting, and it is up to us to really define the appropriate utilization of this technology.

All of the in-person and online attendees, thank you for also taking the time and being part of this meeting today, and I would be amiss without thanking the A/V crew who are now probably watching in the back, so thank you, guys and ladies, for the contribution of making this meeting a success.

And with that, this is the quiz that Andy offered to put forward. So what is the FDA docket number that you all have to search for? And I see a bunch of iPhones going up to try

to take a picture of it. Please provide the feedback. You don't have to memorize this information, obviously, it is available, it is at our link for the workshop, but we look forward to it. You have about 29 days, and we'll look forward to actually collecting this feedback. We will get together, we promise we will get together with our CDMI colleagues, we will analyze the feedback and we will draft a white paper that talks about the summaries and some of the discussions that we've had throughout the day and what will be the future steps for us to move this technology forward.

And with that, thank you very much.

(Applause.)

(Whereupon, at 5:23 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PUBLIC WORKSHOP - ORTHOPAEDIC SENSING, MEASURING, AND ADVANCED REPORTING TECHNOLOGY (SMART) DEVICES

April 30, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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SHAYLAH LYNN BURRILL

Official Reporter