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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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PEDIATRIC MEDICAL DEVICE DEVELOPMENT

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10903 New Hampshire Avenue
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Silver Spring, MD 20993

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M E E T I N G

(9:00 a.m.)

DR. PEIRIS: Good morning, everyone. Hopefully, you can all hear me. If everybody can start taking their seats. I just want to say thank you very much to all of you for making it out today. For those of you who do not know where you're at, you're at the Pediatric Medical Device Development public meeting, just in case.

We have a pretty amazing turnout today. I'll see if I can make this work. Great. We have a Webex, and we have an in-person audience, and we've got more than 875 people registered, which represents a great deal of interest in this topic. So, again, I just want to thank all of you for convening today, connecting today, coming together to help bring your expertise, your experience, and your talents to this topic of pediatric medical device development.

Before we get started, I want to go through some housekeeping issues, and the most important thing is how many people have downloaded CrowdCompass? Great. If you haven't downloaded CrowdCompass, please go ahead and do the download now. It's pretty quick and easy. This is a first for our FDA public meetings. We'll be utilizing a mobile app for audience polling, and we'll start the audience poll right after my introduction session. So, if you'd like to participate in the audience poll, please go ahead and download it now and make sure it's working. All of the speaker bios are available on there, the schedule's available on there, and any other interesting information that's going on with respect to social connections are also available on there. So please take a moment to go ahead and download.

During the question and answer session, the CrowdCompass app can also be utilized for submitting questions, so people that are on Webex can submit questions through your Webex client. If you're using CrowdCompass and you're in person and you'd like to submit

a question without coming up to the microphones, you can definitely go ahead and do that. If you'd like to come up to the microphones, that's fine as well, but we want to develop as much connectivity and interactiveness throughout the meeting as we can, so please feel free to utilize all of those electronic media.

Before we get started, I was asked to make sure that I read this. "Participation in a public meeting by an individual or organization does not imply any endorsement by the Food and Drug Administration." We certainly want to create an open environment for education and discussion.

And if you'd like to submit comments to the docket, docket information is available here. The slides that are running throughout the break will also provide you with the docket information. And I believe those of you who have Webex should be able to see this during the breaks as well.

During the breaks and lunch, if you haven't ordered lunch yet and you'd like to order lunch, you can order at the Sodexo kiosk out there. If you order early, they'll be able to have everything ready for you by lunchtime. You will be limited in terms of not being able to go into the campus area, so this might be the simplest way since we only have about an hour for lunch today to go in and have lunch if you haven't brought your own.

All right. So why don't we get started with the official process? So why are we here today? We are here for all the children across the country whose lives and whose families' lives are dependent on medical devices. We live in an era of unprecedented advancements in medical technology. The interplay of medicine, science, regulatory science, and technology allows for us to create an environment where medical devices can safely and effectively make a difference in so many lives. The FDA believes that children in special populations should have access to medical device advancements that serve their complex and unique needs.

When we take a look at this information up here, we see that medical devices approved and developed for children are relatively less common than those approved for adults, and we recognize that medical devices that are specifically designed, evaluated, and approved for children can certainly make a positive difference in their care.

Over the last 10 years, PMA and HDE devices have been increasing at a relatively significant rate, and part of this is due to processes and policies that have been put into place through CDRH. We have been able to facilitate innovation and public health via these processes.

But when we take a look at this chart a little bit more closely, we see that medical devices approved for adults are growing at a rate about three to four times more often per year than pediatric devices. And, most importantly, when we take a look at the data over the entire 10 years and we normalize this information of percentage of pediatric approvals against total percentage of devices approved, we see that there hasn't been much significant change overall in the number of pediatric devices or the percentage of pediatric devices. We recognize that the reasons for this, and I'm sure I don't have to tell any of you all of this, there's a myriad of issues that certainly factor into why pediatric devices aren't approved and available as easily and often as for adults.

The FDA has been supported by Congress to put together this public meeting through the FDARA legislation, and there are five areas that Congress asked us to focus on, and I'll clarify those. It's basically improving research infrastructure and research networks for pediatric device development, appropriate use of extrapolation, appropriate use of postmarket registries, increasing FDA assistance to pediatric device developers, and identifying current barriers and incentives to pediatric device development. And those are the areas that we'll be focusing our time here on.

What we've done is taken those five topics and put them into a broader construct to

allow for a more robust conversation, and that construct basically involves the three areas of the public meeting today. The three main sessions will be Optimizing Evidence Generation, Creating Regulatory Value and Simplicity, and Developing a Supportive Marketplace. We recognize that some of those topics that the FDA or that Congress requested certainly will overlap throughout some of these sessions, and that's expected.

Before we get started with the three main sessions, we have an introduction session, and we have a great esteemed panel of speakers for us, and what I'll do is give you a brief introduction to that introduction session, and it's categorized in three areas.

Big Needs for Growing Children: We'll have leadership from the American Academy of Pediatrics representing and lobbying for children and representing pediatric professionals across the country and across the globe, speaking to us about why we need medical devices for children. In addition to that, we have leadership from AdvaMed, one of the major trade organizations providing that perspective as well. It's wonderful when organizations of that caliber that are significantly involved in this process are able to align and come together, so thank you very much.

After that, we have Dr. Kurt Newman, who is a pediatric surgeon and CEO and president of Children's Hospital Health System. Dr. Kurt Newman will be providing us a perspective; the way that I look at is it's like during college where the senior professors provide the freshmen, like myself, with the information that's most relevant, and Dr. Newman would be telling us about why pediatric medicine is the cutting edge, why it truly is pushing the envelope of medicine forward. It's not the type of medicine that maybe all of us think about, which is child visits and lollipops, but truly pushing the envelope with respect to medical advancements.

Then we have FDA by the Numbers, and that presentation will be provided by Dr. Mary Clare McCorry. I've been privileged to work with Dr. McCorry, who is an AIMBE

Scholar, and she has done a great deal of data collection and reviewed this information, so we can clarify all the details for you about pediatric-specific approvals at the FDA during the past few years.

After that, we have Michelle Tarver, who is an ophthalmologist and epidemiologist and running our strategic priority and collaborative communities, will give us a concept outline of the Collaborative Community Strategic Priority, and then Dr. Dennis Lund, CEO and CMO of Lucile Packard Children's Hospital, will be providing us with some information regarding the resources available at pediatric academic medical centers across the country, a potentially untapped resource that we really can begin to collaborate with more effectively.

The last session of the introduction will include the technology issues, and what we want to get into here is why size no longer matters, and that's the fundamental point, that it really isn't an issue of technology that may be limiting things but perhaps other aspects of the ecosystem that we really need to be working on. We have Dr. Kevin Maher, who's a pediatric cardiologist and director of Nanomedicine Center in Atlanta, who will be giving us a talk about that.

Bakul Patel, the director of our digital health program, will bring in concepts regarding our digital health program and the precertification process.

And then we have a virtual presentation from Dr. Anthony Chang from California, who will tell us a bit about how pediatrics will be practiced in the future and the influence of technology on pediatric practice. Dr. Chang has been a national and international leader in artificial intelligence and augmented reality and has brought together leadership in pediatrics to help clarify the path forward for pediatric medical practice.

The first session of this afternoon will be Optimizing Evidence Generation. I won't go through too much of the details for each of the sessions, but I'll allow each of the session

chairs to provide that information. Dr. Doug Silverstein, a pediatric nephrologist and reviewer with CDRH, will be chairing that session. Through each of the sessions, we'll have one of the chairs give you a broad overview of the session, the session highlights and goals, and help manage the conversation during the session.

Our second session will be starting tomorrow morning and that is on Creating Regulatory Value and Simplicity. The regulatory value and simplicity session will be chaired by Eric Chen, who is the director of our HUD/HDE program and also the director of the Pediatric Device Consortia Program.

And, finally, we'll end tomorrow with the session on Developing a Supportive Marketplace. The intent here is to discuss the economic and financial issues relevant to pediatric medical device development, and that will be chaired by Cara Tenenbaum, one of our senior policy analysts.

So, at the end of tomorrow, we'll have an integrated panel discussion that truly is intended to bring together concepts and topics discussed throughout the 2 days to help us begin to focus on the strategies that can make a difference for pediatric medical device development, prioritize those strategies, consider the short-, medium-, and perhaps long-term goals that we have and the resources necessary to implement those types of strategies.

I truly believe that if we can work together, we can foster a system that supports technology innovation to serve the complex needs of children, and that system can certainly accelerate medical device development for all Americans.

I want to take a moment here to thank all the people that have participated in developing this meeting and to bring this agenda together. We've had both internal and external people that have done a great deal of work to bring this together. I appreciate the work from a lot of our external collaborators, including the AAP, AdvaMed, academia, along

with many of our internal people, so many volunteers that have come together today, so I thank all of you for helping make this meeting a smooth meeting and a very quality meeting.

I also want to take a moment to highlight the picture in the center here. This is one of the joys I feel, in my profession that I have. This is Julianna, and this is a picture of Julianna when she was in the NICU many years ago. I had the opportunity to help care for her before she was born, during her perinatal period, and years afterwards. She had a very tough time in the ICU, but technology in the right hands with the right management and education can certainly make a difference in lives of children like Julianna. And today Julianna is doing exceptionally well and is having a fun time at school. I get updates from her family on a regular basis. So, I just wanted to share this with you. It's been approved by her parents; they're very happy to be part of this.

So, I want to thank all of you, and I'm sure that children like Julianna and children in the future and families of children in the future who will be actually needing medical devices thank all of you for coming together today and helping us with this important topic. So, thank you very much.

(Applause.)

DR. PEIRIS: We'll get started right away with the audience poll question. Hopefully, everyone's had an opportunity to download the CrowdCompass app. Has anyone had trouble or any issues? Great. So we'll go ahead and start with the first audience poll questions, and these poll questions are really not intended to be anything serious or significant, but really just to begin to focus you on some of the topics that are coming up over the next few talks, and this first one is more intended to ensure that the process is working smoothly for everybody.

So, our first poll question is "Have you ever used or developed a medical device

indicated for pediatrics?" Not too tough of answers: yes, no, or don't know. I'll give you guys a few seconds to answer, and if you go right into the poll area and just hit Poll, it will take you right to the opportunity to answer the question.

(Audience poll.)

DR. PEIRIS: Lia has been kind enough to help us run our CrowdCompass process today, so we'll see if this all works, and again, this is going to be a first, so we put quite a bit of effort into ensuring all of this connectivity runs well. So, Lia, do you want to try to see if you can bring up the answers?

(Pause.)

DR. PEIRIS: Hopefully, this will work. It worked during the trial run, for sure. That always happens, right?

(Off microphone comment.)

DR. PEIRIS: Surveys unavailable. That shouldn't happen. Hopefully, if you try to reenter. So, it looks like the majority, at least, of everyone in the audience has had a chance to be involved with pediatric medical device development, and for those of you who haven't, today will be an opportunity to meet with many people who actually have done that. So, let's see if the second one works a little bit more smoothly, then go back to the poll --

(Pause.)

DR. PEIRIS: I think we've got one more poll, right?

(Pause.)

DR. PEIRIS: Honestly, this all worked much faster during the trials. So, our second poll question is "What percentage of high-risk devices, which usually include premarket applications and humanitarian device exemption applications, were approved in the past 10 years with a pediatric indication?" And that's 10%, 25%, 50%, 75%, or 90%. So go ahead

and take a couple seconds to answer. And this one you actually had a brief insight into already during my talk, and Dr. McCorry is going to do a more detailed dive into that shortly.

(Audience poll.)

DR. PEIRIS: It looks like everyone's answered or almost answering, so why don't we go ahead and try to get up the answer site? Great. So, it's interesting that people have erred on the smaller side of this, which I think is partly a part of the reason why we're here, but we have about 24 to 25%, as I demonstrated in that 10-year normalization graph that reflect pediatric indications for medical devices, PMAs and HDEs.

So, those are the first two poll questions. There's more exciting questions to come, and we'll do a poll question right before or right after each of the breaks. So right when you get back in, sit down and we'll try to do a poll question to get everybody focused again and get on with our talks.

And can you go back to the regular screen again? We have our first session, which is this introduction session, and the focus of the session will be Big Needs for Growing Children, and our first speaker is Mark Del Monte, the CEO of the AAP, so thank you very much, Mark, for coming and giving the talk. And since we have so many esteemed speakers today, we've provided all of their bio information in the app, so you can take a look at that information, and we'll try to make sure that things keep running smoothly in between transitions so we don't spend a lot of time introducing everybody.

Mark, the stage is yours.

MR. DEL MONTE: Oh, thank you so much, Vasum. Thank you so much. I am so delighted to be here. This feels like a very important moment in time, and I just want to begin by thanking the FDA team, the planning group, and all of the people around this room for being here and being a part of this. This has been a long journey in some ways, and it

seems like we can accelerate if we are working together. I look around the room here, it feels a little bit like Thanksgiving; there are some people who have been working on this together for a decade, 2 decades, at least 15 years, and then I see a lot of new partners, and so all of that is very, very exciting. So, let's get right into it.

The American Academy of Pediatrics is the organization that you know. We are a professional organization of 67,000 members. Our membership includes primary care physicians, pediatric medical subspecialists, surgical specialists, academicians, hospital-based physicians, community pediatricians, and all the like. The important part of our membership coming together around an initiative like improving the landscape of pediatric medical devices is because it is central to our mission. The mission of the AAP is to attain optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults. To accomplish this mission, the AAP shall support the professional needs of its members.

The history of the Academy is that it was born out of advocacy in the thirties, designed to improve, in large ways, the health and well-being of children while at the same time improving the care in the one-to-one clinical interactions in every visit with every family and every patient. I'm really excited to be here today to talk about this. I see a lot of AAP members around the room; thank you for being here. If you're not an AAP member, we need you, so please join us. We'll be happy to have you in this conversation.

As we detailed in our policy statement in 2016, "AAP Off-Label Use of Medical Devices in Children," pediatric patients requiring medical or surgical devices have unique needs relative to their adult populations. As you know, fundamental differences in diseases, defects, growth and development, metabolic differences, physiological changes, differences in the nature and course of disease and other factors require medical and surgical interventions that account for these differences. We say all the time that children

are not just small adults. If you design an adult system and try to fit children into it, it never works. However, unlike drugs, there is no requirement in current law that medical and surgical devices be studied in children as a routine part of device development.

The AAP has championed pediatric drug laws, the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act, since their inception. PREA generally requires that for a new drug or drug formulation, if the disease or condition for which the drug is indicated occurs in children, a company is required to study that drug in a pediatric population. Additionally, BPCA provides an incentive for drug companies to conduct studies in children by permitting an additional 6 months of market exclusivity for that molecule. To date, 738 drug labels have been revised with new pediatric drug information as a result of the hard work and partnership of these companies under the law of BPCA and PREA.

AAP has been proud to be the primary advocate behind the initial passage of BPCA and PREA but also the initial passage of the Pediatric Medical Device and Safety Improvement Act in 2007. We strongly support the law and the innovations that it's made, but we acknowledge that it has not gone as far as we had hoped. Unfortunately, among high-risk medical devices that have improved over the recent years, few are labeled for children younger than 16. This must change, and that's why we're here today. We're here to discuss opportunities and barriers to the development, approval, and labeling of pediatric medical devices.

AAP was proud to champion the idea for this meeting last year in the FDA Reauthorization Act, and I'm optimistic as I sit here today and look at the sessions and the participants. We have some of the best innovators and smartest minds here ready to work together to solve these problems. As we learned in 2004, when AAP began a conversation with a multi-stakeholder group of experts, the conversation can be similar today and tomorrow to really throw the ball as far as we can, to think as big as we can, take nothing

off the table, come up with some new and innovative and impactful ideas.

One of the things that we're most proud of from the Pediatric Medical Device Safety and Improvement Act is the Pediatric Device Consortia program. Progress happens when the federal government is committed to improving the status quo and when they find willing partners in industry and academia. The pediatric medical device consortia program is an example of just how that can work.

Since its inception in 2007, the PDC provides grants to nonprofit pediatric medical device consortia which assists scientists and innovators with technical and financial resources to improve the number of medical devices available for children. The seven consortia have assisted in advancing the development of more than 1,000 proposed pediatric medical devices, 1,096 to be precise. Eighteen of those devices are now available to children. Congress's investment in the PDC program has enabled the consortia to leverage that investment to raise more than 150 million dollars since 2009 in federal and non-federal resources funding that work.

Many of the consortias are here today, and I applaud them for their work. I also want to highlight the team at FDA, who has made this program such a success over the last years, especially Eric Chen, Debra Lewis, and Linda Ulrich. Thank you for your work. Maybe we can get FDA to triple its investment in this program as part of the outcome of this meeting today.

In the meantime, off-label use of medical devices in children continues to be a necessary and appropriate, but unfortunate, reality for pediatricians and pediatric surgical specialists. Our goal must be to significantly decrease the off-label use of devices in children so that children are as much as possible using devices that are designed for them and studied in pediatric populations.

We've been here before. Twenty years ago, the vast majority of drugs, more than

80%, used in children were used off label without data on their safety or efficacy. With changes in statute, FDA regulation and guidance, FDA's internal infrastructure, and the support of many of the stakeholders around this room, that number has been reduced to approximately 50%.

As we think about how we really need to do this in medical devices, I hope we can look at the options that those laws provide us and more. We need to come up with new, ambitious ways to engage and build support among stakeholders and to optimize pediatric device development.

This meeting is a first step in an important conversation that we're very excited to be having. I look forward to our discussions today and over the next 2 days working with all of you to ensure that children have access to the safest and most effective devices. The Academy of Pediatrics is a long-time partner in this, and we will maintain our partnership with industry, with academia, and with our members going forward.

Let me close where I began, first of all by showing off my niece Avery; that's her Fourth of July outfit. Let me close with a thank you. It takes a lot to pull off a meeting like this, and it takes a lot to garner the kind of minds that are around this room. We can do this if we work hard, keep children in the forefront, keep children as our north star, and overcome the regulatory barriers, market incentives, and scientific barriers to future pediatric device development.

Thank you very much.

(Applause.)

DR. PEIRIS: Thank you very much, Mark.

Next, we have Bob Kroslowitz, who is the CEO of Berlin Heart and the chairman of the pediatric working group of AdvaMed.

Bob.

MR. KROSLOWITZ: Thanks, Vasum. On behalf of AdvaMed, I'd like to thank the organizers for inviting us to participate in this meeting. My title, the title of my talk, is the same as Mark's. I feel like this should be a rebuttal or something, but I think we have a lot of the same ideas and a lot of the same things to say.

For those of you who are not familiar with AdvaMed, AdvaMed is the largest trade association for medical technology in industry, representing manufacturers of medical devices, diagnostic products, and health information systems that are transforming the healthcare through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMed's nearly 400 members manufacture the vast majority of all medical technology products sold in the U.S. today.

Our mission is to advocate on a global basis for the highest ethical standards, timely patient access to safe and effective products, and economic policies that reward value creation. Most importantly, and relative to this meeting, is the mission of the Pediatric Medical Device Working Group to monitor and address issues related to pediatric device development, regulatory review and approval, and postmarket surveillance by promoting innovative solutions and policies that advance the health of the pediatric population.

Okay. So why do we need medical devices for children? In 2013 there was an article published in the *New York Times* that discussed how medical devices fall short for children. "The development of surgical tools and medical devices designed for children," the author states, "lags a decade behind device development for adults. The lag, say experts, can be blamed largely on economics. Innovation in medicine is driven by need, but also by the market. Big markets have lots of folks developing devices, but small markets like the pediatrics market" does not. "So, for decades, pediatric surgeons and other specialists have had to make do, using adult-size devices 'off label' in children. They might improvise and chisel out their own smaller surgical tools in workshops or jury-rig devices to squeeze into

their tiny patients. Always, they contend with the extra challenges that come with using a device that's not quite right."

However, improvise is not a word that parents want to hear from their child's doctor. Another article published in the *Boston Herald* discussing the same challenges described the case of a small child who had an adult device implanted to treat her faltering heartbeat. The device's large battery bulged so badly under her ribcage that she struggled to sit upright until her first birthday. Indeed, the pediatric device sector is fraught with challenges.

Mark Throdahl, President and CEO of OrthoPediatrics Corporation, a company whose focus is on the development of pediatric orthopedic products, has noted, however, that great challenges beget great rewards. "There is an emotional component to these surgeries that is just nonexistent in the adult space," Mark states. "Our products end up being used half the time in a child with cerebral palsy. These products can enable a child confined to a wheelchair to live without pain and can enable other children to walk normally for the first time. Is there anything really more compelling than enabling a child to walk?"

In 2007 Congress passed FDAAA, the Food and Drug Administration Amendments Act, which included, under Title III, the Pediatric Medical Device Safety and Improvement Act of 2007. Title III requires the FDA to report annually on the number of applications for a medical device that includes description of any pediatric subpopulations that suffer from the disease that the device is intended for and the number of affected patients.

Review of the FDA's reports to Congress over the past decade show that there have been 380 approved medical device applications. Of the 380 applications approved, 56 were approved to treat, diagnose, or cure disease that occurs in the pediatric population. However, only 21% of the approved were with an indication for a pediatric population, and only 2% of the applications approved were solely for use in the pediatric population,

confirming the disparity in the number of medical devices approved for children.

To promote the development of medical devices in a pediatric population, the FDA has provided incentives and guidance that can facilitate pediatric device development and the earliest and broadest patient access to beneficial medical devices. These initiatives and guidance include the Early Feasibility Program, the extrapolation and leveraging of existing clinical data to support the approval of pediatric medical devices, the Expanded Access Program, the pre/postmarket balance guidance, and the acceptance of clinical data from studies conducted outside of the United States. However, a large gap still exists between the idea and the clinical application for pediatric medical devices, mostly due to the significant development and regulatory costs with insignificant financial return.

The FDA has brought together today a diverse group of thought leaders and innovators. I hope that over the next 2 days we will be able to identify creative solutions that are required to bridge this gap and move the field of pediatric medical devices forward in a meaningful way.

For our part, AdvaMed and its members, who produce the vast majority of healthcare technology purchased annually in the United States, and the Pediatric Medical Device Working Group, are committed to developing innovative solutions and promote creative policies that will result in increased availability of medical devices specifically designed and approved for the pediatric population. We and our industry partners are committed to working with all stakeholders to ensure that children have access to safe and effective medical devices in a timely fashion.

We have developed what we believe to be a comprehensive list of regulatory, tax-related, and reimbursement proposals for consideration that we can create incentives to develop pediatric devices that we're happy to share with all of you; however, I have time to highlight only a few, including facilitation of Harmonization by Doing via the International

Medical Device Regulators Forum by creating a global network of trial sites for pediatric-specific devices; designation of pediatric devices as breakthrough devices providing priority application review; development of specific pediatric device review team of individuals with medical and population-specific expertise within CDRH; supervisory review of all pediatric device applications to ensure the least-burden approach; and development of guidance for reverse extrapolation, which will allow the use of data collected during pediatric medical device studies to support the approval of adult indications.

Tax-related and reimbursement proposals include the establishment of pediatrics research and development tax credit program; providing pediatric device development commercialization credits; providing reimbursement for pediatric devices based on safety and early effectiveness data and continue reimbursement while data is collected to demonstrate safety and efficacy; and requiring 3 to 5 years of Medicare coverage for pediatric medical devices with an additional requirement that at the end of this period CMS makes a coverage recommendation that Medicaid must follow.

A clear example of why we need these incentives or desperately needed is the Magnetic Mini-Mover, a device developed by Michael Harrison and the team at UCSF. This simple pediatric device is intended to spare pediatric patients with a sternal deformity, known as pectus excavatum, from a significantly invasive surgical procedure that is associated with a long and painful recovery. A small magnet is placed under the sternum, which is pulled outwards by another magnet that is mounted on a metal bar that sits outside of the chest.

Dr. Harrison shares in an article published in the *Journal of Pediatric Surgery* that "Our experience with the development of this device and the conduct of the trial required to bring the pediatric device to market suggests that most potentially beneficial or even lifesaving devices aimed at orphan pediatric markets will make it to patients only after a

lengthy, arduous, and expensive process."

We must do better than this. In a recent newsletter from the AAP Section on Advances in Therapeutics and Technology, the section's chair, Mitchell Goldstein, states, "We should make sure that when we have discussions with industry, that we dive into the issues that are important to them and help them address what they feel are the impediments in the development process. The environment for development is probably better than it has ever been. For our patients to benefit, industry must be motivated by the opportunities to develop in the pediatric space."

At a recent JLABS event on pediatric medical device development, Vasum Peiris shared the following provocative thought: "Imagine a world in which children have access to innovative medical devices at the same time as everyone else, a world where medical devices are designed and evaluated for their unique needs, a world with the right ecosystem that supports explorers and innovators to engage, sustain, and innovate in the pediatric medical device space. This world really doesn't exist. It probably seems as close to getting to Mars or trying to populate and colonize Mars. I think we can get there. We just need to take the right steps."

So why do we need medical devices for children? I recently received a picture and a note from a parent of a child who was supported with one of Berlin Heart's pediatric devices until she was able to receive a heart transplant. "Hi, Berlin Heart. So, this happened today. Just thought I'd send you a little reminder of how important your work is. Thank you for all you've done to give kids like Juniper so many firsts."

In closing, I'd like to leave you with this quote from Nelson Mandela. "There can be no keener revelation of a society's soul than the way in which it treats its children." I hope that these words will inspire everyone attending this meeting in our discussions over the next 2 days.

Thank you.

(Applause.)

DR. PEIRIS: Thank you once again, Bob.

Next, we have Dr. Kurt Newman, president and CEO of Children's National Health System.

DR. NEWMAN: Well, thank you, Vasum. And to you and Commissioner Gottlieb and all of the others here at the U.S. Food and Drug Administration, thank you for organizing and hosting this important meeting. You know, today, for me, it was a first. As long as I've been in Washington and driven up and down New Hampshire Avenue, I had no idea what was here. And now I understand why we've lost so many of our great pediatricians to the Food and Drug Administration, including Susie, who I used to take care of with patients 30 years ago at Children's National. Best to say, I've been at Children's, as part of a children's hospital, for over 30 years now, most of that as a pediatric surgeon; I became Chief of Surgery and then 7 years ago had a great honor of being asked to be the CEO. Vasum referenced me as being the old professor.

(Laughter.)

DR. NEWMAN: I'll have to talk to him later about what that actually means, but I'm honored to have that role, but from what I remember of the old professors that I had, it gives me liberty to talk about whatever I want.

(Laughter.)

DR. NEWMAN: I know he said that I should talk about the great landscape and future and the frontiers of pediatric medicine, and they're all there, and there's lots of people in this room that know that landscape. And I'm honored to be asked to address this audience, and I've got great friends here and another CEO of one of the terrific children's hospitals in this country who also is a pediatric surgeon, Dr. Denny Lund, here from Packard

Children's at Stanford. I think even that suggests a trend, that there's a growing recognition of the importance of pediatric medicine, of pediatric surgery, devices, and the role that children's hospitals, for example, can play. And I'm really excited to see all of you come together. A meeting like this even 10 years ago, there might've been 20 or 30 people, because we're all trying to make the impossible possible.

Bob, your company, the pictures you showed, and I saw this up close and personal as a pediatric surgeon, Berlin Heart kept one of our children alive for 9 months until they could get a heart transplant. It's just, you know, the impact of that. And she waited, and then she got her heart transplant. I mean, this is, you know, almost made for television, but got it on Christmas Day. And the impact that that had, not only on that family but our whole hospital, because that's one of the frontiers, we see the impact that a device and technology can have on a family, and it just allows us all to join together to celebrate miracles like we saw in that picture. So, thank you for your work not only with the company but with AdvaMed. It's pushing the frontier forward.

It's really heartwarming to see this passion and all of the advancements to help children get the devices they deserve because there's been a long-time perception that a lot of people held that serious clinical care and research aren't needed in children the way they are in adult settings, if you can believe that. And I think partly it's because children are generally viewed, by most people, as being healthy. They don't understand or know all of the issues that children can face, and I think we all understand that that perception isn't true, but that perception has guided so much of the investment we've made, whether it's in the government, in private industry; wherever it is, children are not just invested enough.

And we've heard that that's starting to shift. Both Bob and Mark talked about that, and a lot of that is being driven by families pushing and advocating and accelerating the novel therapies. But as we'll talk about later in this conference, the commercial progress

just hasn't kept pace, and medical devices, although there's change, still lag behind, 5 to 10 years behind the technology advances for adults. And even more troubling, within children in general, you see that there's an unmet need for the smallest children, the 2- to 12-year-old, and for too long pediatric clinicians have had to become accustomed to improvising for adult devices for children, and I saw that myself as a pediatric surgeon. I remember the early days of laparoscopic surgery where we had big instruments and trying to fit them into small babies. Robotics is the same way even today. And that begs a question that I ask myself, you know, where's the pediatric voice? How do we fire up the pediatric voice, and where is the children's perspective? And I've got a disclosure to make. I even wrote a book about that; here it is.

(Laughter.)

DR. NEWMAN: Because, you know, I just was so passionate about how do we change the mindset, how do we change how people view children and investing in children? Now, you're a sophisticated group, but I'm always having to educate people about how children are different and how to change the conversation, and it's critical for all of us here to elevate this fact, that children need a tailor-made technology because there's so much happening, these frontiers, we call it prenatal pediatrics, maybe you call it fetal medicine, but that's a whole new frontier that we'll hear about. Genetics, brain and brain science, and then when you bring imaging into that, think about what we could do to tackle the issues of mental health that 20% of children face. So that's why it's really the best way to tackle these issues in children to ensure a healthy adult population.

Now, I wanted to create a culture that focused on that, and having this children's hospital, and there's others that are on the same path, to develop a stronger culture of innovation at Children's to apply just as much passion to the research questions as we do to the medical care and importantly tie it to its commercial potential. And I'm glad my

colleague who is on the board, Ed Connor, is here to help us make that transformation. And we've got major philanthropy to create a pediatric device institute, create a symposium, and develop some big ideas that just weren't being addressed in children, how to make surgery more precise and less invasive, how to eliminate pain in children. Symposiums have now developed out of this, and I hope I'll see many of you at the sixth annual innovation symposium next month in Philadelphia, which is a day before the MedTech Conference.

We're also part of one of these consortiums, and I think this is a great example of partnership with the FDA's National Capital Consortium, and my colleagues from the University of Maryland are here, which we jointly share with Bill Bentley and Lex Schultheis. It's awarded more than 30 device companies and supported 80 other devices, and many of these have received FDA clearance. And actually two of them now, and you know how hard this is, have gotten introduced in the hospital supply chain, Velano Vascular, and who would've thought that the needleless IV, you wouldn't have thought about in adult, but that's how working in children forces innovation and creativity.

So, I understand all the challenges that are inherent facing the startups and entrepreneurs who make up the majority of pediatric device developers. I understand the lack of interest from venture capitalists that don't see the immediate ROI that comes from helping kids compared to adults, and that's a constant struggle to overcome. You really need a thick skin to deal with that.

But I think, as a pediatric community, we have some inherent values that bring us together. And one of the other wonderful things is the culture changes, and you see the incredible number of young people that want to get involved with children, and that's why I'm so hopeful and I'm so optimistic about what's happening with pediatric medicine. Every organization represented here is doing something and, you know, I know the timer is going off, but I'm the professor so I get a little extra time.

(Laughter.)

DR. NEWMAN: Because, you know, it's the partnership and collaboration because we've got to come together because, you know, we're fighting uphill, but that's a great place to be; that's an exciting time to try and overcome these challenges together.

Here at Children's National in Washington, we feel like we're in a great position. As I mentioned, we've got the FDA here, I think the NIH is starting to look much more proactively toward children's health, and there's a lot of, in all of the institutes, moves forward with that. And I think it's these multi-sector partnerships that will be the next great fundamental idea as we move forward, as Vasum talks about, thinking about this like a mission to Mars.

I think in the future you'll see a big idea I want to talk to you about, which is at the old Walter Reed army medical campus where we look to create a pediatric research and innovation campus for children that will bring institutions and organizations together right here in the sweet spot of innovation with the FDA, the NIH, the patent office in Washington, D.C.

I think this is just an example of what can happen. I look forward to fostering collaboration and an approach that brings together all of the federal agencies, universities, the pharmaceutical industry, because we could really make a lot of progress with that and mitigate conditions. And this is the fundamental concept of pediatrics, that with early detection and all of the things that are coming forward in science, medicine, technology, early detection and intervention, we can either prevent, delay, or stop adult diseases from happening, whether it's mental illness, whether it's cardiac disease, obesity, diabetes, all of those chronic conditions. We just got to turn the system on its head a bit, find ways that people are incentivized to tackle those things because our reimbursement and the incentives are all the curing things and not preventing things. So that's a fundamental

challenge to all of us, to really change that mindset, to be able to bring these things in early and avoid all of the pain, complications, and issues and cost of adult chronic disease. That's where pediatrics really can play a role. Wouldn't it be a gratifying outcome to see that? I think that, you know, as I said, right now the competition for dollars is intense. We need to find ways, open access, coming together, collaboration, to take those resources and harness them across the entire sector because that's the way I think we can bring these medical breakthroughs from the laboratory to the bedside faster and more efficiently.

Thank you very much. I'm excited to hear more from the rest of the panel, and I look forward to talking with you during the rest of today and tomorrow. Thank you.

(Applause.)

DR. PEIRIS: Thank you once again, Kurt.

Before we get on to the next couple of FDA talks, I just wanted to recognize Dr. Jeffrey Shuren, who is the Center Director for CDRH here. Thank you, Jeff, for making the time to attend this important meeting.

Our next speaker is Dr. Mary Clare McCorry. Mary Clare, I wanted to take a moment just to recognize her. She has been working with me through the AIMBE Scholars program this year, and I'm hoping that it's been as much as a privilege for you as it has been for me. Mary Clare has been instrumental in helping get this very bandwidth intensive meeting together, go through a lot of data and other projects that we've had that we've worked on together, so I just want to give a special thanks to all the efforts that you've put in, thank you very much. Mary Clare will be giving, as I mentioned, the FDA numbers and facts and topics regarding pediatric versus adult medical device development over the last few years.

DR. McCORRY: Thanks, Vasum. Well, I hope you guys all had your coffee and you're very awake because we're going to be going through a lot of numbers and facts, and as we go into the next 2 days, we wanted to make sure that you guys had an idea of what the

numbers and facts were on pediatric medical devices at the FDA.

Now, just a quick disclosure: I'm funded by the American Institute for Medical and Biological Engineering. I'm an AIMBE Scholar that's placed working with Vasum this year, which has been a pleasure.

So, my presentation will focus on numbers and facts, but I wanted to start things off by just giving a little bit of legislative perspective. What you see here outlined is some of the key legislation that has affected pediatric medical device development and innovation, and you'll hear more about these over the next few days, and I'll be referencing back to these throughout my talk.

Now, what is the definition of pediatrics? At CDRH, pediatrics is defined from birth up until the 22nd birthday, and there are several subpopulations within that. There's neonates, infants, child, and adolescent, and today I'll be talking about a group within adolescent called transitional adolescent, which is from 18 through 21 years of age.

Now, in 1976 the Medical Device Amendment Acts created a tiered risk-based classification with regulatory requirements that are gauged to the risks that you see outlined in this table right here, and low to moderate risk devices are cleared through the 510(k) pathway with most Class I, low-risk devices being exempt from 510(k).

High-risk devices are considered Class III and are evaluated for safety and effectiveness under FDA's premarket approval process where manufacturers must supply evidence providing reasonable assurance of safety and effectiveness to obtain FDA approval to market a device in the United States. And throughout this talk, I will be referring to these devices approved through this process as PMA devices.

Now, another device type I'll be talking about today are Humanitarian Device Exemptions (HDEs), and in 1990 the Safe Medical Devices Act established the Humanitarian Device Exemption pathway, and this was established to encourage the development of

devices that treat or diagnose rare diseases or conditions, and devices that receive an HDE are exempt from the effectiveness requirement I mentioned on the last slide for PMAs. Here manufacturers are required to show that probable benefit outweighs the risks of using the device. This pathway is especially relevant to our conversation today about pediatrics because pediatrics are often considered a small population.

In 2007, through FDAAA, the Pediatric Medical Device Safety and Improvement Act required FDA to annually report to congressional committees, and among a number of other points, the FDA was required to report on pediatric indications for use in PMAs and HDEs.

What you see on the right is a snapshot of the most recent information collected in fiscal year 2017 for devices approved through CDRH. Out of 66 total PMA and HDE devices, 62 of those devices or 94% of them had a pediatric subpopulation that suffered from the disease or condition that the device is intended to treat, diagnose, or cure. Out of those 62 devices, only 18 of those devices had an indication for use in the pediatric population. Moreover, only 11 out of those 18 devices were indicated for use under the age of 18.

Now, over the last 10 years, these reports started back in fiscal year 2008, so now there's 10 years of data. Over the last 10 years there have been more innovative technologies that have been coming to market. Overall, there's been an upward trajectory in the total number of PMAs and HDE approvals approved per year; however, adult approvals have been increasing at a faster rate than pediatrics where the number of approved PMAs and HDEs in adults increased at a rate of 3.8 per year compared to the number of devices with pediatric indications, which increased only at a rate of one device per year.

Now, when this data is normalized by the percentage of total PMA and HDE devices with an indication for pediatric patients, you see that despite the slow increase in the

number of pediatric devices per year, there is a stagnation overall in the percentage of pediatric approvals over the last 10 years, and this is evidenced by the lack of significant trend that you see in this linear fit. While overall there are more innovative technologies coming to market, and adult approvals are increasing at a faster rate than pediatrics, there has been no proportional change in the percentage of devices indicated for pediatrics. And on average, 24% of devices are approved with a pediatric indication.

Now, I wanted to evaluate this a little bit further and look at those that were indicated for pediatrics, and what you see here is a grouping by youngest age indicated, and since 2008, more than half of PMAs and HDEs indicated in pediatrics were indicated for use over the age of 18, which is that green population that you see, and whereas only 15% over the last decade were indicated for neonates and infants combined, so the pink and the purple groups.

Now, the HDE pathway, in particular, was intended to benefit small populations such as pediatrics, and we do see that a higher proportion of HDEs with a pediatric indication, roughly a third of applications since 2008, were indicated for use in pediatrics. That compares with the 22% we saw for PMAs.

Now, getting a Humanitarian Use Device to market is a two-step process. The applicant must first obtain an HUD designation and then submit a Humanitarian Device Exemption application. In the blue line you see the number of HUD requests received, and in the red line you see the number of HUDs that were ultimately designated. Sixty-four percent of HUD requests received a designation, and an HDE approval authorizes the marketing of an HUD device for its specified indication for use. Of those that obtained an HUD designation, 21% of HUDs designated continued on to an HDE approval, which is what you see in the green line. And in purple you see the number of HDEs that received a pediatric indication for use, and 34% of approved HDEs were indicated for use in pediatrics.

Now, I mentioned some of that legislation a little bit earlier, and the HDE pathway has been modified in 2007, 2012, and most recently in 2016, and these helped provide some profit incentives as well as they increased the population limitation to 8,000 in 2016. And despite these efforts, you can see that there hasn't been a lot of change in the number of HDEs that are received, designated, and ultimately approved, and this is shown by the lack of significant increase in the rate of rise.

In 2007 the Pediatric Medical Device Safety and Improvement Act also established the Pediatric Device Consortium that you heard a little bit about earlier, and this consortium helps to encourage innovation and connect qualified individuals with pediatric device ideas. On the chart on the right you'll see that this program was authorized by Congress for 6 million, and 2017 was the first year that the program was fully appropriated. In previous years, having not received full appropriation, FDA would provide supplemental funds whenever possible.

The Pediatric Device Consortium have accomplished several milestones, and this is what you see here on the slide, I'll highlight just a few of them, and they've helped support 35 pre-submission meetings with the FDA as well as support 21 Investigational Device Exemptions and 19 medical devices to market through the 510(k) clearance.

The last thing I'll talk to you about is the de novo process, and although Congress did not require the analysis of de novo approvals for the annual report back in 2007, well, we conducted analysis of these because novel low-risk devices are approved through the de novo classification pathway. And this pathway was established in 1997 through FDAMA, the Food and Drug Administration Modernization Act, and the de novo classification provided regulatory authority for FDA to classify devices that were automatically classified into Class III due to a lack of predicate. And back in 1997, the process was that a sponsor would submit a premarket notification through 510(k), then FDA would issue a final decision of not

substantially equivalent due to no predicate, and then the sponsor would be allowed to submit a de novo request, and then FDA would decide whether or not to classify the device down from a Class III into a Class I or II. And that is quite a lengthy process, so this pathway got modified in 2012 through FDASIA, the Food and Drug Administration Safety and Innovation Act, and this established the direct to de novo path which allowed sponsors to submit a de novo classification request to the FDA without first being required to submit a 510(k).

So now, currently, there are two options for de novo classification for novel devices of low to moderate risk. First, you can receive an NSE determination through the 510(k) process and then submit a de novo request to the FDA. The second option is that if you know that there is no legally marketed device upon which to base a determination of substantial equivalence, you may submit a de novo request directly to the FDA.

Now, similar to the data I showed you earlier, we evaluated the last 10 years, starting in 2008, and over the last decade there has been a relatively high number of adult de novo approvals compared to pediatric approvals, and for de novos, 20% were indicated for use in the pediatric population with the remaining 80% being approved for adults. They're general use instrumentation or they remain silent.

So, for this analysis, we wanted to be a little bit more clear on the population identified in the indication for use, and a device was considered what's being called silent here if the application did not specify an age population in their indication for use statement. And over half of the applications were silent on age, and half of those that were silent did conduct studies in a pediatric subpopulation with the other half conducting studies only in adults or not conducting clinical studies since these are de novos.

When we looked at PMAs and HDEs, we found that the majority of devices indicated in pediatrics were indicated for transitional adolescents or pediatric patients from 18 to 21.

Similarly, with de novos, 38% of de novos with a pediatric indication were approved for use under the age of 18, which compares to the 40% we saw for PMAs and HDEs. And over the last decade, 7% of all de novos were indicated for use under the age of 18, which compares to the 9% we saw for PMAs and HDEs. Overall, these data show that a very small percentage of novel device approvals over the last 10 years are approved for use in pediatric patients under the age of 18.

Thank you very much, everyone, and a special thanks to my niece, who managed to stay still for this photo.

(Applause.)

DR. PEIRIS: Thank you very much, Mary Clare.

Next, we have our next FDA speaker, Dr. Michelle Tarver, who will be giving us some highlights regarding our strategic priority on collaborative communities.

Michelle.

DR. TARVER: Good morning, and thank you for allowing me to give a brief overview of our strategic priority.

So, in these times of rapidly advancing science, emerging healthcare challenges and diseases, as well as the increasingly empowered and engaged stakeholders, collaboration is not just nice, it's imperative. In fact, Frances Hesselbein and John Whitehead stated, "As we look around us in a new century, we realize that businesses and nonprofits in today's interconnected world will neither thrive nor survive with visions confined within the walls of their own organizations. They need to look beyond the walls and find partners who can help achieve greater results and build the vital communities to meet challenges ahead." It is this spirit that is embodied in our strategic priority of collaborative communities. In our document, we state that it's a place where public and private sector members proactively, not reactively, work together to solve shared problems as well as problems that may be

unique to specific members of the community and that it fosters an environment of trust and openness so that members can feel free to communicate their concerns.

Another characteristic of the community is collective responsibility because it's important that we all feel engaged in tackling the topic in order for the community to be successful. The effort is not confined within the geographical borders of the United States but extends internationally.

Our steering committee here at CDRH has worked to further flesh out the definition and provide greater granularity. So, in addition to saying that it's a public and private sector effort that proactively works together to accomplish goals, we have emphasized some of the characteristics of trust, openness, respect, and empathy. It's important to note that these communities will not be convened by the FDA, but FDA is a member of the community sitting arm in arm next to other members to tackle these challenges.

The communities are not envisioned to be stood up and then disbanded but instead to exist indefinitely to produce deliverables as needed and tackle challenges with broad impacts. They should include diverse, relevant organizations and individuals impacted by the topic. This also includes patients, which are children, their parents, patient advocacy groups, healthcare systems, hospitals, health professionals, as well as industry and the regulators.

The key takeaway from our effort is that FDA intends to support, leverage, and/or adopt the solutions that emerge from the collaborative communities as appropriate within the context of the statute, regulations, agency priorities, and the best interest of public health.

FDA's role as a member on these collaborative communities is to help foster community spirit and responsible choice to solve problems and proactively build for the future. Our goal is to help establish at least 10 new collaborative communities by the end

of 2020. You may be asking, well, why collaborative communities? FDA collaborates a lot of entities. Our rationale for going forward with collaborative communities is because there's a number of challenges that may be ill defined or where there's no consensus on the definition of the challenge, and working together to shape and hone those definitions is necessary with a group as a group effort. The challenges and outcomes may be complex or multidimensional; the partners are interrelated. Previous incremental or unilateral efforts to address the challenge has been ineffective. Therefore, in an effort to prevent duplication and to optimize the effort, collaboratively working together with different perspectives, different experiences, resources, power, and expertise is needed.

This slide shows the characteristics of what we envision a collaborative community to have. As I said before, it's a sustained effort. The leadership should be broadly distributed, the community should have the values of trust and empathy, reciprocity and inclusiveness. The community should cultivate an ethic of contribution, and effective informal communication is necessary. In fact, it's been said that the poison of effective collaboration is politeness.

So, one of the potential deliverables that we would like to see out of these communities, it could possibly be recommended guidance or consensus standards and range all the way to having a culture change or a paradigm shift.

So, if there's any additional questions about collaborative communities, we welcome them, you can send them to this email address. You can also visit our CDRH strategic priority website where we'll be updating and providing insight to new products that we've developed to help foster the establishment of these communities, so please stay tuned, and we welcome any comments or feedback you all have. Thank you very much.

(Applause.)

DR. PEIRIS: Thank you, Michelle.

And next we have Dr. Denny Lund, the interim CEO for Stanford Lucile Packard Children's Hospital.

Denny.

DR. LUND: Good morning. Thank you, Vasum. As he mentioned, I'm Dr. Denny Lund. I'm also a pediatric surgeon. Currently I occupy the role of interim president and CEO at Lucile Packard Children's Hospital Stanford. I suspect that the choices of having the CEOs of the children's hospital that is closest to the federal government and the children's hospital that is closest to Silicon Valley were not a random choice, so I do appreciate the opportunity to be here. In my real life, I am the Chief Medical Officer at Lucile Packard Children's Hospital. I rise to make a case for the important role that children's hospitals have in pediatric device development and for the need to promote and support enhanced collaboration to see successful and rapid implementation of these devices in children.

I'm an amateur historian, so I have to start with a little historical vignette, and this is a story many of you know. Dr. Sidney Farber, the famous pathologist at Boston Children's Hospital, started the field of pediatric cancer chemotherapy. In 1959 he and colleagues began a demonstration project that showed that actinomycin D plus radiation therapy were effective in the treatment of Wilms tumor, a pediatric kidney cancer. Despite very promising results, it took him years to accrue enough patients to publish those results. This and other early chemotherapy trials in childhood cancers led to the realization that childhood cancers were so rare that pediatric providers had to band together to share their results.

The Pediatric Cooperative Group System was a clinical research program that started in 1955 with a consortium focused on childhood cancer research. By the end of the 1990s, there were four funded cooperative groups, and by 2004 pediatric groups voluntarily merged their efforts to create what is now known as the Children's Oncology Group. And as

an example of this approach, going back to the example of Wilms tumors, there are actually only 400 new Wilms tumor patients a year spread out across the entire United States.

Children's hospitals, importantly, have to work together to collaborate and share their outcome data. Fortunately, our children's hospitals have been absolute pioneers in the development of cooperative studies, and as a result of this effective cooperation, many childhood cancers, even though rare today, have cure rates approaching or exceeding 90%, including Wilms tumor. Pediatric providers and hospitals did this because it was the right thing to do for children.

So why do I share this history about cancer chemotherapy with you at a pediatric device development symposium? It's quite simple. Children represent only a fifth of the population, and fortunately, most children are healthy. The U.S. children's hospitals that deliver complex care, hospitals like Dr. Newman's and my own, treat only about 6% of the pediatric population.

Also, it's important to note that children's healthcare spending in the United States now represents only about 9% of total healthcare spending and the majority of this actually for well child care. This fraction of spending for children is actually continuing to shrink as baby boomers age and need more medical care.

Thus, a device that is likely to be invented and developed specifically for a childhood indication, for example, a ventricular assist device for infants and babies, and I know there are a number of you in the audience for whom this is a special project, will not generate a strong business case for its development that is likely to attract private funding. Common innovation development technology transfer methods that we use so often in medicine cannot find a good base, a good business case for these orphaned devices. Thus, I would argue that children's hospitals have to step in to assist and invest in pediatric device development, if they can.

One other example I want to share of the success resulting from the cooperation of children's hospitals is in the area of safety and quality. The Solutions for Patient Safety, our children's patient safety organization, has made incredible progress in lowering the hospital-acquired conditions and the incidence of serious safety events as a result of cooperation between our children's hospitals.

Fortunately, many children's hospitals are stepping up to the realm of device development. At Lucile Packard Children's Hospital Stanford, faculty and staff actively participate in what is known as the Stanford Byers Institute for Biodesign, an incubator specifically for medical devices that is a partnership between our Stanford Schools of Medicine and Engineering. Packard also participates with five other children's hospitals in the Institute for Pediatric Innovation, which works on device and drug development.

We're not alone. Other children's hospitals also have major efforts in device development and innovation. Boston Children's Hospital has the Innovation and Digital Health Accelerator; CHOP has the Philadelphia Pediatric Medical Device Consortium; Cincinnati Children's has Innovation Ventures; and here in Washington, at Children's National Health System, there is the Sheikh Zayed Institute for Pediatric Surgical Intervention, just to name a few.

There are many other such consortium of children's providers who, by working together, are improving the outcomes for children in trying to bring pediatric devices to clinical use. For example, just in the area, again, of ventricular assist devices, which I mentioned earlier, there are a number of multi-institutional trials attempting to bring this technology safely to the smallest of our patients. My favorite, personally, is one called the PumpKIN trial.

In this one situation, since there is a decided shortage of organs available for small children needing heart transplantation and waiting times are often very long, a safe device

that will offer a bridge to transplantation for these small patients will save lives. In fact, new and novel devices have the potential to save or improve as many or more children's lives as pharmaceuticals and other innovations.

Just as with pediatric drug protocol development, through collaboration and cooperation between our children's hospitals and our children's healthcare delivery systems, we can safely and efficaciously develop and generate the necessary data to quickly approve the best device ideas coming out of our children's hospitals. I urge the FDA to support efforts for development of pediatric medical device and collaboration between children's hospitals and providers to provide device efficacy in order to rapidly bring them to clinical use. And I urge the children's hospitals to be open to further collaboration around devices. It's complicated but has the potential for the tremendous benefit for children, and it's the right thing to do.

Thank you very much.

(Applause.)

DR. PEIRIS: Thank you very much, Denny.

Now we have a few minutes for question and answer to the panel. I just want to take a quick moment to say thank you once again for all the panelists.

(Applause.)

DR. PEIRIS: In case you're wondering how to ask a question, you can come up to the microphone, you can ask your question on CrowdCompass, and people that are watching us on Webex can ask questions through the Webex cloud forum or straight through CrowdCompass as well.

MR. GRANT: Thank you. My name is Lee Grant with Medtronic. I have a question for Dr. McCorry, and that is regarding the de novo process. On that breakdown, can you tell me, is there one particular area where you're seeing more products being cleared through

the de novo? I know from the orthopedics branch, we haven't seen anything really come through orthopedics. Do you see that changing, and what can industry do to help make the de novo process more successful? Thank you.

DR. McCORRY: Thanks for your question. I'm trying to think back to the data that we went through. So, I know that for PMAs and HDEs there's a lot of those devices are coming from the cardiac division as well as a lot of in vitro diagnostics. I can't quite remember for the De Novos where many of them are coming from, and I apologize.

DR. PEIRIS: Yeah, most of the De Novos do come a spectrum across our device applications, but as Mary Clare mentioned, a majority of our pediatric-specific medical devices certainly come from a few areas, and that includes cardiovascular, orthopedics, endocrine, so I think those are the key areas in terms of where there seems to be interest from industry in developing.

DR. KOH: Chester. I just want to make a quick comment in addition to Mark's presentation that, as we all know, the American Academy of Pediatrics has a very strong voice here in Washington, D.C., a lot of the work secondary to what Mark's been doing in the Washington, D.C. office for many years. I've been asked how do non-physicians and surgeons become part of AAP, and there actually is a mechanism that's through the section of advances in technology and therapeutics where you can be a section affiliate for $40 a year and still be a member of AAP. So, I just wanted to make sure everyone knew that.

DR. PEIRIS: Thank you, Chester.

MR. DEL MONTE: And thank you for that commercial. I appreciate it.

(Laughter.)

UNIDENTIFIED SPEAKER: Thank you for the interesting information so far, and my question is about when we use some devices, we go and can then medications such as anticoagulation and antibiotics with the adult patients especially. So when it is a case with

pediatric patients, do we treat the devices along with the medication as an integral part or the separate part, because we want to extrapolate information from the adult patients to pediatric patients, and during the process, like do we treat the medication also as an integral part of the devices when translating it from the adult patients to pediatric patients?

DR. PEIRIS: Sure, I just want to say thank you for the question, and your question certainly goes into some details in terms of device and medical product reviews. We'll try to keep any of those questions for later, and we're happy to speak with you offline, and we can also give you information regarding who to contact to get more direct answers for that. And we'll provide you with that information right afterwards.

DR. ESPINOZA: Thank you. Good morning, my name is Juan Espinoza. I'm from Children's Hospital Los Angeles. I had a question for Dr. Tarver relating to the collaborative communities. Could you give maybe some specific examples of what kinds of communities you're looking to support and what kind of instrumental support the FDA might support, might provide to support those communities? Thank you.

DR. TARVER: So not to make the obvious obvious, but we're speaking at this meeting for a reason, so we definitely want to encourage the development of a pediatric medical device collaborative community. In terms of the approach, obviously, there's a lot of other different potential communities that could potentially start. One of them is the, if you'll look at our strategic priority document, Dr. Shuren has described some of the potential communities that we are looking at. Some of them revolve around real-world evidence, next generation sequencing, digital health; there's a lot of different topics in which these collaborative communities could exist, but pediatric medical devices is very high on our list as one that we would like to see established, and we're speaking today, hopefully, because there's so many stakeholders in this room that could work to establish that type of a community. Did I answer all of your questions?

(Off microphone response.)

DR. TARVER: Thank you.

DR. PEIRIS: Lynne, I think you might be next.

DR. YAO: Thanks. Lynne Yao, FDA. So, Vasum, thank you for getting such incredible heavy hitters here on this panel in the morning, and so I wanted to take the opportunity to ask each of you on the panel, since it's such an important opportunity, at the end of this 2-day meeting, if you could pick one thing that you think we need to do at FDA or with the assembled folks here, what would that one or two things be? I'd really like to hear what the panel has to say about that.

DR. PEIRIS: Lynne, you're stealing our questions for the end of the day.

(Laughter.)

DR. PEIRIS: No, please feel free. I'll open it up to the panelists, whoever would like to take it.

MR. DEL MONTE: Yeah. Thanks, Lynne. I would say a couple of important things about our goals at AAP for this meeting: One, I'd like for this to be a historic moment in time. I'd like to think about the time before this meeting and the time after this meeting and so that we can hold this as a marker of a new initiative that we can work on together.

There are a couple of things that we know to be true about pediatric populations who need devices. One is that they are very small populations. That's a good thing. The idea that a few number of children need these kinds of very highly tailored implantable and surgical devices is not a bad thing; that's a good thing. Most kids are well. We are not going to be able to change the markets, nor do we want to change the market drivers for devices. What we need to do is correct for them.

So how do we think together in a big way to solve the scientific, technological, and market issues that are keeping us sort of from making big progress? I don't think that there

is going to be a magic answer. If we had had a magic answer, I think we would've deployed that already. I think everybody is, in good faith, working hard. What we are likely to get is a similar model as we found when we were working on the Pediatric Medical Device and Safety Improvement Act, which is a collection of important but discrete activities where the sum is greater than the parts. And so, if we can leave at the end of this meeting with a plan, a pathway forward, an agreement on a set of activities that we can work on together, I would declare that a tremendous success and would look forward to committing the resources of the AAP to working on that plan with you.

MS. CHOWDHURY: So, we have a question. Oh.

DR. NEWMAN: Are we just going with that one answer?

(Laughter.)

DR. PEIRIS: Go ahead, Kurt. You're good to go.

MS. CHOWDHURY: Go ahead. Sorry about that.

DR. NEWMAN: My big idea that I'd love to see is an evolution of the perspective of that devices are just not to fix things that have already happened, but we really begin looking into and promote investment and creativity, innovation, and devices is part of that, around prevention and around identifying the issues that begin in pediatrics. Although kids look healthy, but they become adult chronic type diseases, and I'll go back to mental health or diabetes, heart disease, obesity, and that we look at the technological advances in a different way and build conditions of a market that promotes that. And I think that would be just a huge move forward to think about children differently, and it is becoming not only what's happening now, but what happens in the future.

DR. PEIRIS: Thank you very much, Kurt.

Any other thoughts from the panel?

(No response.)

DR. PEIRIS: Should we go to the Webex question if that was in line?

MS. CHOWDHURY: Yes. Thank you, Vasum. This question comes from the CrowdCompass app, so I'm just going to read it out loud. So why didn't we hear more specifically about pediatric devices during the MDUFA VI negotiations? And to follow up on that, could a user fee incentive move, such as for devices, move then for the review queue and provide incentives?

DR. PEIRIS: Perhaps if none of the panelists want to take this one, I'll try to provide, for those of you who aren't familiar with the MDUFA negotiations, the MDUFA process, there's an opportunity for all the stakeholders and the communities to work with the Agency and clarify what the priorities are, and part of that process also entails clarifying how user fees will be utilized to attain those priorities. So, I think the conversation regarding pediatrics and pediatric medical device issues during the MDUFA negotiations is certainly something that is open for discussion and can be brought to the table by the stakeholder community.

MR. DEL MONTE: Vasum, just a comment. So, the, you know, industry has already committed through MDUFA IV to providing over $1 billion in user fees, so I have to imagine that we could somehow find some support for the pediatric ecosystem.

DR. PEIRIS: Thank you, Bob.

Dr. del Nido.

DR. del NIDO: Thank you, Vasum. First of all, congratulations on putting on a fabulous program, and the response is amazing. I think we have a unique opportunity in that we have some leaders of provider organizations as well as providers as well as industry representatives here.

When I hear the presentations, there's a huge gap in not so much Class I devices but the more advanced Class II and Class III devices. And I think the significant need is for data,

clinical data, in order to support the evaluation and advancement of these devices into the clinical world. The pediatric challenge, obviously, is the numbers, but if we have several provider representatives here and we have industry, perhaps one of the goals can be finding out what would actually enable the collection of data so that devices could actually go forward. I don't think there's any shortage of ideas, and I think innovation is just as great in the pediatric world as it is in the adult world and, in fact, probably more so because people in pediatrics have always been innovators; we always had to be. But how do you get that idea, particularly in a critical device that's a high-risk device, evaluated and approved? That's what I'd like to hear, how the partnership between industry and the providers can actually enable them.

DR. PEIRIS: And while the panelists, if you guys have any thoughts, I'll just kick this off. This was not a plant. Dr. del Nido, thank you for setting up our next session, which will be specifically focused on optimizing evidence generation and all the issues surrounding that, so if any of the panelists have any thoughts open to taking.

MR. DEL MONTE: I'll just make a brief remark now. I think the academy is certainly open and interested in discussing novel ways to collect evidence to generate data that would demonstrate safety and efficacy in useful ways. I think the small populations problem is an opportunity for innovative approaches.

Having said that, however, I think one of the principles that we have to hold the line on, and we have been very strong about this, is that what you do not want is a lower standard for children or pediatric populations than you want for adults. And so as long as we can keep the standard high, as high as adults, and from our perspective, it should be higher than adults, right, because they're more valuable, but in any case, at least as high as an adult standard, then that's the place I think we have to stay. We would not want to take novel approaches to the place where you really don't have confidence that what's going on

is not experimental or marketing a device that is not well demonstrated both for safety and efficacy, so I think we can agree upon that as a principle going forward. Outside of that as the principle, then let's be creative and thoughtful about how we gather and evaluate evidence.

DR. TARVER: I'd also like to mention that it's important to include the parents and the children in the conversation. A lot of challenges we have in collecting clinical trial data is people don't want to participate, and so having them as part of the design process is imperative to ensure that the trials are designed in a way that encourages them to want to work with the investigators and with industry to generate the evidence that's needed to help make those decisions.

DR. del NIDO: I think parents are going to be your biggest advocates, honestly. I think most parents who see their child and you tell them this is the only option, I can't imagine a parent saying no. But I think there's genuine challenges with doing that, and I'd like to hear from industry.

Bob, I think you're going to make some comments.

MR. KROSLOWITZ: Yeah, certainly. I mean, AdvaMed, in all of our discussions and our proposals, you know, our thought process was to lower the burden and not the bar, right; that's not what we're looking to do. And I was most intrigued this morning by the presentation that Michelle gave on the collaborative community, and I am really convinced that this is how we will move things forward is collaborating, industry together, medicine together, and the FDA. For the pediatric space, you know, it's such a small space with such a small number of patients, and we have to find innovative ways to generate data and meaningful data, right, not just generate data; we need to generate data that's meaningful and is really going to do something to move the field forward, and I really think that that is going to be very important to us moving forward.

DR. NEWMAN: I think Dr. Lund gave a nice sense of a model where you could take these pediatric consortiums that the FDA has promoted and are really taking hold and then look even more broadly about how those consortiums come together and whether it's the model of the children's cancer group or patient safety, but you can see knitting those together would get you the kind of numbers.

I think one of the things that happens, though, is that the commercial aspects of it sometimes get in the way of that, and so it's not as open and collaborative as it needs to be to get the numbers. And so that would be a hurdle that would need to come down to create that kind of collaboration across companies, across these consortiums, to get clinical trials, and there are some organizations here that we'll hear about later that are working on that.

DR. PEIRIS: Thank you.

Denny.

DR. LUND: Yeah. Kurt, thanks. I would agree completely. I think we're at a tipping point because, you know, the history of drug development and device development has been really dominated by looking for the next great blockbuster. Guess what? In pediatrics there aren't going to be any blockbusters; the volume's not going to be there, so we just need to get over that and figure out how we can work together analogous to what we've done in a number of areas in pediatrics.

DR. PEIRIS: Thank you very much.

We'll take one more question, and I apologize, just to keep things on track.

MS. RAZJOUYAN: Fatemeh Razjouyan with BD, and my question is for Dr. McCorry. First, I'd like to applaud you for pulling the data together. I know it's not an easy task. Knowing the majority of medical devices, including innovative devices, go to market through the 510(k) pathway, why your presentation excluded devices from that pathway.

DR. McCORRY: Yeah, that's a great question. You know, so the first part of the presentation and the easiest answer is that Congress mandated the analysis for PMAs and HDEs and, you know, simply, you know, we wanted to start this analysis focusing on the innovative devices, which is why when we had a little bit more bandwidth, we expanded this out to de novos. I think that certainly it would be very interesting to get that data for 510(k)s; it's just a little bit more complicated to parse out the data for 510(k)s, whereas with PMAs, HDEs, and de novos, it's a little bit more clear cut to do that analysis. So it's certainly something we'd like to do, but figuring out exactly how to do it and do it right would be the next step.

DR. PEIRIS: Thank you very much, Mary Clare.

Thank you very much for the robust conversation, and I hate to cut things off, but it's my honor, I think, for all of us, we have Dr. Scott Gottlieb, Commissioner for the U.S. Food and Drug Administration, here to say a few words.

Dr. Gottlieb.

DR. GOTTLIEB: Thanks a lot, and thanks for giving me a few minutes to share some thoughts with you. I appreciate the opportunity to be here. This is a great turnout, and we're delighted to have you all here. I think it really shows how much interest there is in this issue and how important it is that we were able to turn out such a robust group, not just here in person but online. I'm pleased to join you for this important discussion about pediatric medical devices, and I want to add my words of welcome to the others who you've heard from this morning.

Today's topic has a lot of special resonance for us here at the Food and Drug Administration. We are living right now in a time of extraordinary scientific medical innovation. We're at really an inflection point, I think, if you will, in science and medicine and also when it comes to public policy. This is giving us enormous opportunities to

strengthen the public health through new innovation. During the next 2 days, I know you're going to be discussing a number of these advances and the opportunities that they afford us to develop successful new pediatric devices. And as you do that, I hope you'll take note of the special role that FDA has played in the development of these kinds of products and in helping to make sure that they're safe and effective.

And consider, for example, when you go outside, the historical exhibit that sits just outside this room, it documents a traveling exhibit put together by the FDA in 1933 called the Chamber of Horrors, and there's also some online video of this exhibit, and for those who follow my Twitter feed, I've been tweeting it out as well. It was designed to highlight many of the dangerous products that were on the market at that time. That exhibit was instrumental in getting Congress to pass in 1938 the Food, Drug and Cosmetics Act, which granted the FDA the authority to remove these types of products from the market.

One such product that you'll see in the exhibit is a device that its manufacturers advertised as an effective treatment for diphtheria and other ailments for children. It was called a Vapo-Cresolene apparatus. It used kerosene to heat a chemical that produced coal tar vapors for children to inhale. Not only was there no evidence that the device worked, but I think in all likelihood it's fair to say it probably caused more harm than help to those who were using it. We've come a long way since then, and today more than ever, we recognize the unique needs of children, and we're working to encourage the development of safe, effective medical devices designed specifically for pediatric patients.

We have a lot to do when it comes to addressing the specific needs of the pediatric populations, and we know that, and there are still far too few devices on the market designed specifically to treat, diagnose, or cure diseases in children. And as you heard this morning, over the past decade, despite legislation from Congress and regulatory improvements by our Center for Devices and Radiological Health, novel devices designed

and evaluated and approved for pediatrics is only about a quarter of those for adults, and the majority of pediatric approvals are not for children under the age of 18.

In 2017, and you've heard some of these statistics, I know already we approved 66 devices through the PMA and HDE pathways. Only 18 were indicated for use in a pediatric population, and of the remaining 48 approvals indicated for adults, 42 were determined by internal pediatric experts to have the potential to treat, diagnose, or cure disease which occurs in a pediatric subpopulation.

But we know that there are a lot of challenges surrounding the development of these pediatric medical devices. One issue is the obvious one, that there are physical differences between children and adults that can effect development. There are also higher costs sometimes associated with the development of medical devices for any affected population of a small size and especially those designed for a pediatric market. These are just some of the practical roadblocks to overcome.

We're committed here at FDA to doing our part; we're committed to supporting the development and the availability of safe and effective pediatric devices and to encourage device innovation for medical conditions that impact young populations. And we have a number of current initiatives underway to advance these goals, some of which I know that you're familiar with.

For one, we're increasing the number of medical devices with labeling for pediatric patients by incorporating known information about device effects in other populations to support pediatric indications. We're also recruiting pediatric experts for FDA advisory panels whenever there's a reasonable likelihood that the device under discussion could be used in children. And we're collecting data on the unmet needs of pediatric medical devices and the barriers to the development of new pediatric medical products and devices, and we're taking new steps to protect children who participate in clinical trials. In addition, FDA

has made significant investments in pediatric expertise. The Office of Pediatric Therapeutics has a full-time pediatric ethicist and a neonatologist, and we've added the Division of Pediatric and Maternal Health in our Center for Drugs. Other programs like the Pediatric Device Consortia Grant Program and the Humanitarian Device Exemption pathway have helped foster the approval of a number of pediatric-specific medical devices and devices with pediatric indications, and our incentive programs for orphan diseases, which are designed to help meet the needs of smaller medical populations, can also be helpful in advancing pediatric medical devices and other products.

We're also working hard to integrate NEST, our National Evaluation System for health Technology, and to incorporate real-world evidence generation strategies in these challenges. This can provide us with the data that promotes the kind of patient-centered benefit-risk approach that supports pediatric medical device development, but we can and need to do more. Public meetings like this one are essential to supporting these efforts, and we look forward to hearing from those with a direct stake in this process.

So I want to thank you again for joining us for this meeting and for your continued engagement on this issue. We look forward to hearing your comments, and we look forward to continue to work closely with you and with all the stakeholders in this community to help see how we can advance technology to serve the complex needs of children and other special populations and accelerate the development of safe and effective pediatric medical devices.

Thank you for your time today. Appreciate it.

(Applause.)

DR. PEIRIS: Thank you very much, Dr. Gottlieb.

So, with that, we have about a 10-minute break that we'll take now, and then we'll come back, and for anyone who hasn't downloaded CrowdCompass yet, please go ahead

and do that, and we'll start our next session with another audience poll question. Thank you.

(Off the record at 10:49 a.m.)

(On the record at 11:04 a.m.)

DR. PEIRIS: Thanks, everyone, for getting back in, and I didn't realize I had so much power.

(Phone recording.)

DR. PEIRIS: What you're hearing is our move towards technology. We are contacting Anthony Chang, who is our third speaker and will be giving a talk virtually. I'll try to stop talking while this is going on.

(Pause.)

DR. PEIRIS: All right, I think that's my cue. So we'll get this next section started. This is the section that I mentioned earlier about the technology issues and really going into the issue of why, perhaps, technology may not any longer be the limiting factor. To kick off the section, we have Dr. Kevin Maher. As I mentioned, he's a pediatric cardiologist, and no, I didn't just invite all of my friends. But Dr. Kevin Maher is also the director of the nanomedicine program in Atlanta.

So, Kevin, I'll let you kick it off there.

DR. MAHER: Good morning and thanks, Vasum, and thanks to your FDA colleagues for putting on an incredibly important meeting. It's something that's near and dear to my heart. So I don't think I'm doing polling.

(Off microphone comment.)

DR. PEIRIS: I apologize. I think we do have one audience poll question that I mentioned we're going to go through before this next section, so apologies. Hopefully, this will go very smoothly since everyone has their CrowdCompass app up.

So this audience poll question is which age group do you think is the most technologically savvy? There's always only one answer, and it's the answer that you choose, that's the answer. So the choices are 2 to 12 years, children; 13 to 18, considered adolescents; 18 to 21 years, to introduce the concept of transitional adolescents, for those of you that are not pediatricians; 22 to 40 years of age; and 40-plus years of age. So everybody take a moment to tell me what you think which population, technologically savvy.

(Audience poll.)

DR. PEIRIS: Great, 13- to 18-year-olds, dominant win. I think I wouldn't disagree. But, again, these questions are intended just to give you a sense of what your colleagues in the audience are thinking about and feel about some of these topics. As I mentioned, this is that section on technology, so I'll hand it back to Kevin.

DR. MAHER: Thanks, Vasum.

(Pause.)

DR. MAHER: All right, we'll try again. So the title of my talk is I'll talk about why size no longer matters so far as pediatric medical device development, and we talked a little bit about miniature and some nanotechnologies. So I'll talk a little bit about pacemakers, but I think it's just a good overview of what has happened in medical devices over the past 50 years, pretty remarkable technology, and then a little bit how medical devices and technology are interacting, and then briefly some conclusions.

This is sort of the "why" for me, so this is a child in my cardiac intensive care unit. This child is on extracorporeal support, or ECMO, and you can see literally dozens of devices that are being used here, and essentially, everything is some type of modified or absolute adult device that has been used to take care of these kids. So my hospital alone, there's over 200 critical care beds, and if you multiply that by all the children's hospitals across the

country, you can just see the demand and the need is tremendous.

I'm going to talk a little bit about pacemakers, and everybody's heard, you know, Uncle Louie has a pacemaker, and they are really remarkable devices, but if you go back and sort of just see where did this all come from, so back in the '40s and '50s, the devices were these big clunky machines that were plugged into AC circuits. This one's very nice because you can actually have your dinner on your pacemaker.

(Laughter.)

DR. MAHER: And then eventually they went to battery power, but this is sort of early days of Medtronic up in Minnesota. And so you can see the device is still actually outside the child's chest, and then the wires would go transthoracically to help to pace the heart.

This slide represents a lot of years and a lot of development of medical devices. You can see early on the pediatric or any pacemaker device would just be inserted into the heart, and it would just pace. It didn't know what the heart was doing; it would just pace whether the heart needed it or not. And then over 50 years the devices became smaller, lighter, and much more capable. It's able to sense the atrium, sense the ventricle, and it can pace. It can recognize respiratory efforts so far as activity, and also, remarkably, you can communicate with these devices noninvasively. And so by simply holding a wand over the pacemaker, you can program the pacemaker, you can figure out what's the battery life, how are the leads doing, change the heart rates, change the interventions on the device.

One thing that has happened over the last probably decade is the big players in this field continue to develop smaller and smaller technologies, and so these are really remarkably small pacemakers that are in use today, one by Medtronic and one by St. Jude. Perhaps the tragedy is these tiny little pacemakers here, they haven't even been tested in children.

And if this was not impressive enough, just so far as developing this technology, it continues to go. So this is actually work at Stanford, and so now these devices are not much bigger than a pinhead, and actually, this is just a device that's in development, but it's been in animal models, but they're able to transmit energy through the chest wall to be able to power this device. And even the next generation is using stem cells to create native internal pacemakers using stem cells. So pacemakers, yes, certainly miniaturization has occurred and you can go down to this thing the size of, you know, a pinhead, and the small little finger there is sort of similar in relative size, so you can see really remarkable miniaturization has occurred. But really what's impressive, I think, so far is this advancement, there's more reliability, safety, capability of these devices and functionality, durability, and quality. And so that's occurred over a 50-year period.

And then really try to take a step back from what allowed this to happen, and there's a lot of advances in a number of different fields, so material science, electronics, manufacturing techniques, computer science, energy storage, and the future, I think, is going to be nanotechnology. So it's all about technology and everybody, you know, there's an exponential increase in technology in this country and really around the world.

So the exciting field of material science really is not that boring because it really does make an impact in everything that's done so far as devices. It has a key role, I think, in advances of medical device development. Metals and alloys are used in almost every medical device. Ceramics are important because they don't degrade in utero. Polymer is very important for 3-D printing and prototyping, biomaterials and composites. And I'm going to move on; I have 5 minutes left.

So energy devices are more efficient; the next generation batteries are being developed. Piezoelectric devices actually generate electricity with the movement of the body, and extracorporeal transmission of power is important. CAD, which is computer-

aided design, and 3-D printing really has revolutionized device development. What used to take months for new devices can be done in hours, days, or weeks. Nanotechnology, I really see this as an enabling science, and it really impacts all areas of science, including biology, chemistry, physics, computer science, material science and engineering. I think I was watching the Olympics when I made this slide.

(Laughter.)

DR. MAHER: This slide is actually individual atoms that have been lined up to spell the word IBM, so IBM was key in developing the scanning, tunneling microscope that allows you to manipulate individual atoms, and that was 30 years ago when that slide was made. Today there's actually computer-aided design for nano-printing, so you're going to actually design structures at the atomic level and print them.

Another new nano application: This really marked advancement in developing of chips for computer production, and so you really are now able to produce a semiconductor from a printed scan of liquid metals. So this will just completely change how chips are made, making computers smaller and smaller and more capable.

Some advanced manufacturing that we've been working on in one of our labs is to use a nano membrane circuit and integrated chips. Just briefly, this is a device that we're working on that you can roll it up, you can put it on the skin and immediately have all your vital signs sent wirelessly to your device.

The difference is just to be able to have something to really try to change how we take care of our patients in a really much more effective and more appropriate manner, getting rid of numerous wires, getting rid of devices that are actually bigger than your patients or a number of wires that are just going to bother the kids.

So, in conclusion, I think getting to smaller devices, the technology exists for a disruptive level of changes in medical devices for children. We can also have improved

safety performance, reliability, and functionality, and it really still needs to be the driving factors. I think the advances in technologies have altered research and development, making prototyping easier, faster, and cheaper. And the final is continued legislative efforts to support pediatric device development essential to the success, because all of the advances in technology, if we don't have the companies and the FDA and Congress really all aligned with the rest of us, I think it would be more challenging to get these devices to kids.

Thanks very much.

(Applause.)

DR. PEIRIS: Thank you once again, Kevin.

Next we have Bakul Patel. Bakul is director of our digital health program. Bakul, you can take it away.

MR. PATEL: Thanks, Vasum. And thanks, Kevin, fantastic talk and the power of technology. I live in this world called digital health, and people ask me, like, what is that, and I really don't know what that means, and so I'm hoping that I will learn from you guys today. But I'll give you a perspective of sort of how I see digital health has evolved in the world of pediatrics, especially for pediatrics, how technology, without actually being so invasive, as Kevin talked about for pacemakers, have actually helped. And I'll touch upon one story that I recently came across and just really moved me. And this actually goes back to the slide that I've created, which digital health is not just about technology but it's about connectivity and also information and brought together with software actually brings a lot more to us than we normally would have imagined.

The story I'm about to share is about autism and, you know, how just the mere fact that nothing else but just the tactile feedback and the feedback that you get from swiping different screens have been used, just purely an iPad can be used to manage people or kids with autism. It was the first story I heard about 6, 7 years ago, and then recently I just

heard about how managing, teaching people skills with this digital native that, you know, Vasum talked about, and we all voted that 13 to 18 years old are more, much more, used to technology and sort of born with that phone in their hand, not the silver spoon, but the phone in their hand, is actually helping to move some of those things that, you know, creating biomarkers, creating, you know, tests, creating, you know, ways for us to manage in a way that we've not been able to accomplish by just human interactions all together. So that's how I think about digital health in this space.

So what is FDA doing in this space? I'll just walk through some of the concepts around the pre-cert program. Vasum asked me, he said, can you give like status of data, where precertification is and how does it like all line up to the world of pediatrics in addition for this overall goal for enabling technology to reach patients, and in this case pediatric patients specifically, and kids in general, before we label them as patients, how do we think about that?

So one of the motivations for this program is we know these technologies will be out there; we know these things will be available for people to be accessed. How does FDA create an environment? And this environment we're trying to create is giving people the confidence not only just in the technology itself but also the people who are making these technologies.

So going back to this concept of if you were to take the organization-based approach, I think we can avail a lot more products which have a higher level of confidence than we would normally see when those products are reviewed in this traditional way. So we're looking for that, sort of the value added with this program we're envisioning. We are right in the middle of creating those boxes that we started last year and filling them in with more concrete ways to start thinking about how those boxes would come across or be built, is how do we appraise a company, what kind of products that would be going to the market

with review or without review and then relying on postmarket, real-world performance of those products itself and the companies' performance as well. We want to take that information and using a database, a data-based sort of knowledge and informing that paradigm is something that we're trying to create.

We bank this entire program on these five principles, and I will take a short minute to walk through them, and I think everybody in this room would probably agree these are the right principles. We have heard it over and over that patient safety is paramount for us. Product quality is paramount as well. And if you go down, the new things that are added to this that are not normally talked about specifically is clinical responsibility, and we talk about clinical responsibilities, people making these products finding a responsible way to deliver products in a meaningful clinical way. What does that mean? We're still working through figuring out, but that sort of nuance. And then we all know connectivity brings cyber risks, interoperability risk, how do you sort of bring that in a responsible way. And the kind of people that we want to promote and have create products and systems that goes to market in a very fast way is with proactive culture.

So when you take these five underlying principles, you would take these five principles and embed them across this picture I showed you in the previous slide, and how do you sort of take that, not just about the organization, not just about the product, but also bringing the real-world performance and tying it all back together is really what we're trying to create as an environment.

We proposed these four different components that builds on this concept of trust, verification, and then transparency. How do you sort of build that in together, and how does a program achieve that in a way that not only allows people to be reviewed, for reviewing the products, but also allowing people to sort of share what they do best?

One concept that I have talked about quite a bit is giving people credit for what they

do best and then enabling behaviors that are good, and which means that if people are doing best, we can give regulatory credit for those people, then we'll enable more of that, which will enable more products to go to the market ultimately. So that's the concept we are driving towards. We proposed in a recent model, a recent model update that we published in June is this concept of we've been talking to a bunch of folks and a bunch of stakeholders, and we came up with the criteria that is FDA defined. We want the companies to sort of see how they can meet them in their own way, which allows freedom for processes and activities and how they sort of manage their processes, and translate that to something that we could understand ubiquitously across different product types and take that to the next level.

We're in the process of building the middle blue box, the dark blue box, and the result/analysis process at this time. So we are in the process of figuring out how can we look at a company and figure out what does that mean to meet those commitments and the domains that we listed.

One important concept as part of the program we want to promote as well is this evolution of knowledge that happens once a product is in the marketplace. It could be any, right? You can think about real-world performance or real-world evidence as just clinical evidence, but you can think about performance as well. Product safety, continuous product safety monitoring, which I can guarantee most technology vendors would be inherently building it into their products as well.

So the concept we proposed initially in the International Medical Device Regulators Forum document where we said, you know, if you know what your product is doing, the evidence that you have, you can go to the marketplace with that claim and then eventually build with real-world performance data back into the product for the next iteration. Allowing that iteration to happen, which is really what is germane and innate to this world

of software as well as digital products, is something that we want to enable.

I won't take too much time, but just working through some of these updates that we provided, we are really looking for people, everybody's engagement, and especially this community who is focused on pediatrics, how can we incorporate them? This is an opportunity now for us to hear from you guys to see this is what we want you to include as part of the concept that you're building. We are on a track to build a version 1.0 of the program or share the version 1.0 of the program by the end of this year in a document, and we would test that entire program next year, 2019. That's sort of the road map we are working towards.

How do we get there, working with the nine participants, allowing people to see how we are testing, what criteria we have developed, and how we get people to sort of input that, give us input to this program is really what we want to do. And this is not going to be done just by us; we want everybody to be engaged in this, and we are looking for input. So if you haven't seen the working model, I would encourage you to go see it now and get back to us on input to the program itself. Thank you very much.

(Applause.)

DR. PEIRIS: Thank you very much, Bakul.

So our next presenter, as I mentioned, is Anthony Chang. Anthony is in California, and the intent here was not to test out our AV capabilities, but fortunately, Anthony gave us the opportunity to do so, and I think it's very apropos considering Anthony is going to be telling us about how pediatrics may be practiced in 2040 and beyond. Anthony has been leading this conference for a number of years and, as I mentioned earlier, is a thought leader in artificial intelligence and augmented reality.

So, Anthony, I think we can all see you. I don't know if you can see all of us, but I'll let you take it away and hope that it all works.

DR. CHANG: Great. Thanks, Vasum, and I also want to give a shout to all the pediatric device colleagues and especially ones from the International Society of Pediatric Innovation, or ISPI, and hopefully we'll continue to converge. So Vasum asked me to talk about the future of pediatrics and gave me 10 minutes. I wasn't sure what to do with the other 8 minutes.

(Laughter.)

DR. CHANG: And I also think that giving a talk at the device meeting of the FDA on AI was a perfect recipe for a disastrous AV attempt to show a slide. So, I just thought I'd focus on one question which I get asked often and it relates to the FDA obviously is, is AI a device? And I think I'd be curious to see what the audience thinks and feels about this, but I think the answer is a very complex one even though the question is very simplistic, but I do think with three efforts we can, perhaps also directly working with the FDA and AMA as well as the AAP, which I have the privilege of doing, I think we can come up with some relatively simple solutions that will not take away the tremendous momentum that you're seeing in artificial intelligence and medicine in general.

So just to recap what's happening in artificial intelligence, as you probably know, the cumulative growth rate of AI in medicine, including pediatrics obviously, is about 30 to 40% for the next 5 to 10 years, so it's just exponentially increasing. And with recent international attention to AI in medicine, particularly China, UK, France, and Russia, so the U.S. is slowly getting a little bit behind, so hopefully we will recognize that in time and continue to push the agenda in medicine with applications of AI. So that's on the international front.

And nationally, strong efforts are being made in computer vision and deep learning to interpret medical images, so that's going pretty well. And a few radiologists are a little bit threatened, but I think they're starting to accept the fact that AI will just be their partner

when they interpret medical images, and that concept will go to pathologists, dermatologists, cardiologists, which is our field as well, because I think with the escalating number of medical images, we actually won't need help to interpret images.

Another big area is decision support, and especially in the light of wearable technology and personalized medicine, I think AI will actually be a tremendous help there as well, and we're already starting to see value proposition in that area as well.

So the upcoming areas that you'll hear about includes things like AR and VR and mixed reality for education and training as well as the use of blockchain for data security. Also, more sophisticated ways of doing deep learning and also the internet of everything, which is a concept of embedding primitive AI into all of the devices. So I think all of these will have a high level of relevance to those of you who are in devices.

So coming back to the question is AI a device, I think we need to do at least three things to, I think, decrease the tremendous burden that we will have to impose on organizations otherwise. So I think the first thing is for those people who are not yet educated or enlightened on artificial intelligence, I think education is going to be very key, and also at the same time, I think we need to promote a much closer collaboration with our computer and data scientist colleagues.

So on the clinician side and the researcher side, I think it's really important for all of us to maintain a basic educational level, and I wouldn't expect all of us to be facile with the intricacies of coding for these learnings, but I think it's important to understand what it is and what the limitations are, which are important concepts, and also promote a closer collaboration with the data science domain in general.

I think, second, for the data scientists, I'm working with several groups to basically demystify the black box reputation of artificial intelligence. And there's a strong effort now to bring about something called XAI, which is Explainable AI. So, again, we all drive cars,

and no one expects us to be a mechanical engineer to the point of understanding all of the details of a car and how it runs, but at least we need to understand the basics to drive a car, and I think the data scientists are starting to appreciate that more and more, and there's strong effort to particularly demystify deep learning, which of all of the methodologies in artificial intelligence, including machine learning and natural language processing, which is how computers and humans will communicate, and cognitive computing, which is what IBM wants and is mainly about, of all the methodologies, deep learning remains to be the most mysterious to the non-data scientists, and we need to reconcile that issue.

And I think the third, perhaps, helpful guideline is that ultimately, just like when we drive cars, although that's being contested now with autonomous driving vehicles, ultimately, I think humans still need to be accountable for particularly the adverse effects.

And as some of you recall, a few decades ago Isaac Asimov came up with the laws of robotics, which I think we can modify for AI in medicine, and that means that ultimately humans need to be accountable for the practice of AI and in medicine particularly, because if you think about it, the wrong algorithm in some ways could be even more dangerous than many of the devices that get approval through organizations like the FDA. And I think, ultimately, humans need to be accountable. Now, by that I mean not just data scientists but the clinicians as well.

So I think it's a tremendously exciting couple of decades coming up. We are already seeing some early dividends, but those are the low-hanging fruits of deep learning and computer vision. I think the much more exciting area to me is going to be AI's influence and involvement in finally delivering, I think, state-of-the-art precision and personalized medicine. So with that, I'll hand, virtually hand back the microphone to Vasum.

(Applause.)

DR. PEIRIS: Thank you very much, Anthony. I don't know if you'll have a chance, I

know you have a full clinic, to stay for a few minutes for question and answer, but if you're able to, please do.

So at this point we do have a few minutes for Q and A, so I'll let you all be thinking about your questions.

Bakul, if you don't mind, I'm going to put you on the spot here. I know you probably had some time to think about this, conceptually at least, but Anthony asked a question, is AI a medical device? Perhaps you can tee that off.

MR. PATEL: Well, first of all, thanks for putting me on the spot.

(Laughter.)

DR. PEIRIS: You're always welcome.

MR. PATEL: I think it's a fantastic question, but I think the question is not just about AI itself, right? So I think we need to think about the foundation and the bedrock of FDA, FDA 101, is intention of that product, right? What does the maker of that product intend to do? And AI for, you know, finding out what groceries you buy next is really not a medical device. So the question really is AI, even when it's intended for a medical purpose, is that a medical device? And I think the answer is self-evident there.

So it's more about that than actually is AI a medical device, right? What you get through an intent, how do you build an intention? It could be through, you know, pen and paper or some other machine or mechanical or non-mechanical type machine or any other software algorithm, but it goes back to the intention. So I would say that a better question to ask is when AI intended for medical purposes is a medical device or not, and I think the answer is in there.

DR. PEIRIS: Thank you, Bakul. That was a well-rounded answer.

Kevin, I think the talk that you gave certainly helps us recognize that technology is advancing quite a bit, as all of us have said, and the opportunity for technology no longer to

be a limiting factor in what is provided for anyone, especially children, is out there. What do you think is the limiting factor these days with respect to getting those types of devices developed for children?

DR. MAHER: Thanks for putting me on the spot as well.

DR. PEIRIS: You are welcome.

DR. MAHER: So I think that when I talk about or think about pediatric medical devices, so much is innovation and collaboration. And so myself, I'm primarily, you know, a clinician and a pediatric cardiologist, but I have a great deal of interest in furthering the development of pediatric medical devices, but I don't have the engineering shops to develop the next, you know, new widget.

And so what has been very successful for our group is the collaboration, and we're very fortunate to be part of the Georgia Institute of Technology, or Georgia Tech, so we have a shared biomedical engineering program at Children's Emory and Georgia Tech. And so that allows sort of access to technology, and what has really been one of the most important things is just getting the scientists, the engineers, and the clinicians in the same room, and that has spawned probably 50 different projects and really has made all the difference for us.

DR. PEIRIS: Yeah. I think you're bringing up the point that Pediatric Device Consortia and other ecosystems of that nature certainly are making a difference and bringing the right expertise together to begin, what I don't want to say is the process of development, but we're at least having that infrastructure being built and laid down, and hopefully, these concepts are being integrated into people's careers moving forward for pediatric device development. Thank you.

UNIDENTIFIED SPEAKER: Vasum, we have our question online.

DR. PEIRIS: Great, thank you.

UNIDENTIFIED SPEAKER: So the question is how does 3-D printing of medical devices impact pediatric medical device development?

DR. PEIRIS: Panelists?

UNIDENTIFIED SPEAKER: Bakul, I think that's you.

(Laughter.)

DR. PEIRIS: Well, I think everybody is familiar or may be familiar with 3-D printing, it's certainly something that has been taking off both in the clinical realms, I'll mention, in the pediatric cardiology world that I work in, it was something that was very interesting when we no longer had to either draw a picture for patients and show them how their three-dimensional dynamic moving heart works and what the problem is for their child, but we were actually able to print a 3-D model developed from scans like MR and CT that you can actually hold in your hand and recognize exactly what's going on, and I think that made a huge difference in moving forward for people to understand what's going on with the heart. If I didn't do that type of work every day, it would be challenging for me to understand it as well, but that's an example of how 3-D printing has certainly affected clinical medicine.

In the technology realms, 3-D printing certainly has amazing potential, and that potential is still being, I think, met both from the technologies for 3-D printers and what 3-D printing can do. And it's not just for medical devices, but also for bringing different technologies to drug development and combination product development. So I think the simple answer is 3-D printing certainly has great potential here.

DR. CHANG: Hey, Vasum?

DR. PEIRIS: Yes.

DR. CHANG: Can I just add to that? I think what's going to be vitally important in the coming decade or two is that we find some way of perhaps using some AI tools to virtually

and continually work together, because what I see slowing down momentum, given the technology explosion particularly in the last 3 to 5 years, is that we are more fragmented and more isolated than ever before. So I always say we're hyper-connected but we're under-communicating. So I'm hoping that perhaps the Pediatric Device Consortium and ISPI, the society that we formed for innovation, can continue to explore ways in which a pediatric neurosurgeon in Boston can work with a colleague or a nurse practitioner in Colombia that are interested in solving the same problems. And, hopefully, with AI and also natural language processing and ways that we can put ideas into the cloud, we can achieve that final sanctuary for innovation and particularly in device development.

And I think the second point I wanted to make was Kevin mentioning the multidisciplinary effect. I think it is more essential than ever before to not just work virtually but also work in a true multidisciplinary fashion, and I don't mean coming together once or twice in a month to talk about a project, but I mean actually go to the other person's world and explore possibilities. And I certainly learn a great deal just learning how data could be assigned to this work and what they think when they do work, and I think that's vitally important that we have a cohort of people that share both worlds.

And, thirdly, I think, as you can see from the topic, the traditional concept of a device is going to change dramatically; it's going to become something that you actually don't see. So nanotechnology and artificial intelligence are good examples of where the concept of a device is going to disappear in terms of physical presence. So I think that's an exciting development in the future as well.

DR. PEIRIS: Thank you, Anthony.

A number of topics there, but I'll maybe just address the simple one of connectivity. One of the things that we're working on here as well, with being the first time at an FDA meeting where we have a mobile app, we are intending for everybody here to be able to

connect with each other. Anthony was demonstrating how we're going to at least have some connectivity at Transcontinental, which is great. I know the other points that you're bringing up, Anthony, certainly are very valuable ones and things that we'll have to consider as we move forward in figuring out how do we most effectively collaborate within the ecosystem. So thank you once again.

DR. SNYDER: Hi. Brian Snyder, Boston Children's. So I have a comment. So I'm involved in innovation, and I'm also a clinician. One of the problems, though, is we have innovative devices that will have an IDE or an HDE, but the insurance companies won't pay for the device, considering it an experimental device even though we may have established this as the standard of care, and an example was the vertebral expandable titanium rib, the VEPTR device, which was pioneering in orthopedics for thoracic insufficiency, but yet insurance companies refused to pay for it, considering it experimental.

As we move into then virtual methods and software, it's going to be even more difficult to convince insurance companies that this is a product that benefits patients but has a cost. Hospitals are unwilling to assume that cost. So how are we going to get insurance companies to be able to pay for these innovations?

DR. PEIRIS: Let me give you the perfect solution. Everybody ready? I think it's a great question, Brian. The topic of how reimbursement and payment influences innovation both across the landscape in medical product development and specifically for pediatric medical device development is an important one, and we will try to address that a little more intimately during our sessions tomorrow, which will focus on marketplace issues, and we have some colleagues from the reimbursement field coming in as well at that point, so perhaps we can get some perspectives from them.

DR. ROY: Shuvo Roy from UCSF Pediatric Device Consortium. So going back to the title of this session, because 21st century technology brings to my mind that a lot of the

technological innovation pipelines originate with some research agencies, research-funded agencies and the National Science Foundation and particularly for medical devices the National Institutes of Health. I'm curious to see how you see those agencies and others as well, Department of Energy and Department of Defense, partnering in the area of pediatric device development, if there's a role for them.

DR. PEIRIS: Yeah, that's a great question, and I think there are number of partners, federal partners and private partners, that are very involved in research development and research funding. I know one of my colleagues, Chris Almond, has recently had some funding from an unusual source for pediatric and general heart disease studies, and that's the Department of Defense, and there are a number of different opportunities in research funding and research grants that all of the agencies that you mentioned do provide. It is an issue of researching or investigating where your research or an entity's research fits in with the priorities of that organization.

Doug.

DR. SILVERSTEIN: Bakul, after working with you on the IMDRF for about 2 years, I'm going to put you on the spot here. So you have done a lot of regulation and discussion about the SAMDs, the standalone medical devices. So for the people here who are thinking about use of medical apps, development of medical apps, innovation, what do you see as the special considerations for pediatric patients and the use of medical apps in that group? In other words, what kind of medical apps may require regulation and what may not? I know that's a long answer here, but (sentence not finished).

MR. PATEL: Yeah, maybe I'll touch on, thanks, Doug. Doug, when I was showing you the IMDRF slide about continuously learning and using real-world data, that was instrumental as part of creating that, so that's where it comes from. But I'll just share with you. I think one of the opportunities, not challenges, but really pending opportunities in

the digital health world is to use technology to meet the special considerations for the patients and the audience that you're reaching to. There's so many opportunities to reach, like what I was talking about earlier, about using the swipe as a mechanism to sort of get people's attention or manage their behavior using technologies to educate people in different areas, or even using that feedback mechanism that's available through those devices and through software and through these technologies, leveraging that is really what we would suggest to look at. Like any other technology, like any other technology, there is actually this challenge about how do you best use them so that it's not harmful. In the case of mobile and digital, I think, because of miniaturization, there are some challenges that we need to consider for the population that you're trying to reach and have the need.

So I think if you want a generic answer, it's the answer that we give to anybody who is creating technologies in any other space. In mobile, because the field and technology is moving so quickly, there may be more things available to you than you are aware of. So just keep that in mind as you move forward or people are moving forward with those things, which may not have been available to you in previous worlds. So just that's an advantage in this area.

DR. PEIRIS: Thank you.

So I think with that, we will conclude this session, and now it is lunchtime. I think everybody has about an hour for lunch, so if you can all plan on being back here shortly in that time, we'll get started with our next audience poll question and the second part of the day. Thank you.

(Applause.)

(Whereupon, at 11:49 a.m., a lunch recess was taken.)

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

(12:52 p.m.)

DR. PEIRIS: Hello, everybody. We're getting ready to get started for the afternoon session. Thank you for cutting your lunch a little short. We appreciate that. Some of our panelists are here already and will be taking a seat, but if everyone's ready and excited, we've got Poll Question Number 4, and if you all can pull out your smartphones and we can do the poll question and perhaps get started from there.

So Poll Question Number 4 is from the following options, which do you think is the biggest challenge in generating evidence to support a pediatric medical device indication? And is that research infrastructure, consent and assent issues, a small sample size, pediatric expertise, or regulatory considerations? We asked for the Jeopardy music, but that didn't work out.

(Laughter.)

DR. PEIRIS: It looks like a few of you are still coming up. Great. So the small sample size certainly wins out, and that's one of the points that always tends to come up. And it looks like regulatory considerations is a close second with research infrastructure, and perhaps those are equalizing as all the answers come in. But one of the good points is we'll be addressing research infrastructure during this talk and sample size issues and some of the comments, questions that came in during the Q and A earlier regarding evidence generation.

And perhaps without further ado, let me hand over the microphone and the wheel to Dr. Doug Silverstein. Doug is a pediatric nephrologist and one of our reviewers at CDRH.

So, Doug, I'll hand it over to you.

DR. SILVERSTEIN: Good afternoon. I hope you all had a nice relaxing lunch. I'm just going to make a few brief comments as we move forward. Could we have the next slide,

please? And a couple more. That's who I am.

And so just very briefly to introduce the topic, I think that a lot of us know, in the pediatric world and the medical device world, that typically the most time-consuming aspect of pursuing a marketing application or getting a labeling change is basically to generate evidence, clinical data. And so in this session, we're really focusing on clinical versus preclinical bench animal data.

And so our session goals are, first, we're going to highlight the program's policies and procedures that streamline evidence generation. We're going to talk a little bit about regulatory paradigms and how we here at the FDA can get a little more flexible. I think we've been doing that, and Randy Brockman is going to talk a little bit about that with our regulatory paradigms.

We're also going to talk about the National Evaluation System for health Technology, also called NEST, and the use of real-world evidence, basically once a device is out there or in any other way that evidence is generated, as used in the community.

And, finally, we're going to talk a little bit about the pediatric clinical trial infrastructure, different ways that we can pursue evidence within that framework.

Second, we're going to develop measurable practices within the current framework specific to pediatrics. So, basically, how do we assess what we're doing both here in the Agency and on the outside?

And, finally, we're going to talk about novel evidence generation opportunities, basically what strategies can you pursue to generate evidence, something beyond the randomized clinical trial, which is the dreaded three words of medicine but obviously very necessary, but we understand there has to be a lot more options for that.

So we're going to start off the session by introducing Steve Anderson, and he is in the pediatric working group at AdvaMed and the CEO for Preceptis Medical, and he's going

to talk about some solutions to barriers for pediatric evidence generation.

MR. ANDERSON: Thank you very much. I'll start out by saying, first of all, there are no easy solutions here. When I saw the topic and coming up with solutions, I kind of rolled my eyes and thought how do you overcome these? But there are things that we can do to make it, to improve this process and that the AdvaMed ped working group has come up with. So next slide, please.

So let me start off by saying I am the CEO of a pediatric medical device company which I founded, but I'm also a parent; I have a son with spina bifida. I should've thought to bring some nice photos of him; his name is Noah. He's had 25 surgeries; he has a very high spina bifida lesion. He is the poster child for childhood special needs and a family with special needs having to navigate the children's hospital healthcare system. And so the reason that I started a pediatric company is because of the obvious needs and unmet needs, I should say, for my son and kids with spina bifida. So I'm coming at this as a role of both a parent and an industry.

I'm going to give a couple of slides about our company, and I'm doing this to give some background and some context as a case study to what we actually go through out there as device companies. But I will start off with one more bit of background, and that is what we have to remember is that adult devices are developed and commercialized because of a profit incentive. The incentives are there. And with children, we have a fantastic group of people at this meeting, everybody here has at least some degree of altruistic intent here, but benevolence and altruism is not enough. You have to have the incentives. Those incentives are there for adults. We have to come up with incentives for pediatric devices. And so what the ped working group has done is come up with ideas on streamlining the process and incentives. So we feel that we need both.

So our company is an ENT company; we have developed surgical instrumentation

that allows ear tube surgery, which is the most common surgery in the world and in the U.S. for kids, to be done without the need for general anesthetic. Older kids above 12 and adults have this done in the office with only topical anesthetic. Younger children are all done under general anesthetic in an operating room because of the need to keep them still and comfortable.

The use of general anesthetic in children is a big flash point in pediatric healthcare, and in fact, at the end of 2016, the FDA issued a formal safety alert that the use of general anesthetic in children under 3 for multiple exposures or long durations can cause future brain development issues. So what we did is we developed instruments that would significantly reduce the trauma and the time it took to do the surgery with enabling it to be done without the need for an operating room and enabling it to be done without the need for general anesthetic.

And so we've got two different kinds of groups that we're doing. We're doing kids, young kids, in the office with nothing but topical anesthetic, and we're doing children that are 24 to 60 months in a sedation area, so both of them reducing or eliminating the general anesthetic. Next slide, please.

So what have been our challenges? So, first, it's worth remembering that it's not just about development again through the Agency. You have to be able to commercialize. If you can't commercialize, you haven't done anything, the product is not going to be used. And so we need to always make sure that our discussions are about bringing products to market and successfully commercializing those products, and that takes significant capital to do this.

Now, I was embarrassed when I looked at the next bullet point, pediatric device companies have been able to procure traditional U.S. VC investment. It's amazing how the lack of one word, have "not," been able to get U.S. VC investment.

(Laughter.)

MR. ANDERSON: So I apologize for that. Ten people reviewed my slides, and we all missed it. But, yeah, we have not been able to get U.S. venture capital, and on top of that, it's not just pediatric devices that are fighting this battle. Device companies, as a whole, have far less access to venture capital than we used to. If you compare the device base to pre-2008, there's about 20% of the venture capital available for devices that there was and we're down 80%. So for adults we're down 80%, and for children's pediatric devices, it's even harder.

So, you know, why have we specifically been unable to get U.S. funding from a VC? You would think reduction of risk, reduction of cost, how can you miss? But that second sub-bullet is the key here. Nobody in the device industry's companies or VCs have been able to make money on pediatric devices. That's the harsh truth that we're dealing with, and the challenge is going to be can we come up with incentives that can push, can push this forward, and that's going to be the challenge, and we've got some good suggestions, though.

There have been no major exits, and in fact, there's only been two ped companies that have gone public. One is represented here, OrthoPediatrics, and then Natus, which is NICU and PICU monitoring equipment, which is slightly different than kind of the classic device world that we live on. So for the companies and the VCs, they're all, you know, the markets are perceived to be too small to make money.

Even though that we had angel, we had angel tax credits and angel investors, we were able to get started, but when it came to commercialization is where we really ran into trouble and we just simply weren't able to raise capital. I spent 2 years in the U.S. VC space trying to raise capital. In my previous companies, I've raised over 150 million in total in venture capital. We just could not get started with this. Just nobody believed in peds. We

had to go China, we got it done through China; we're lucky and we're going to have a shot at success, but at the end, we need these streamlined pathways and tax incentives, and that investment has got to fund development, the regulatory process, clinical process, and commercialization. Next, please.

So I don't have to say this; we just did a poll on this. You know, why are they difficult to do? You have small sample sizes, you have parents, I mean, I'm a parent of a child. My son has been offered clinical studies probably a dozen times. Most parents, unless you don't have a choice, are not really that excited about their child receiving an investigational device. You're far more concerned about being careful with them.

And then the fourth bullet point here I think is really worth noting. Whenever you're dealing with children, whatever it is, we can all talk about the need to reduce barriers but keep the bar in reality. Everybody actually reacts the opposite. The IRBs are more conservative when it comes to pediatric studies, the divisions and the branches at FDA are more conservative. I know they probably don't want to hear that, but that's human nature. Everybody wants to protect children, and they're nervous about it.

So, you know, within what we did, we even, I'm not going to mention any names, but we had to do a 10.75 appeal to get our clearance, and that wasn't easy. We were successful with it, and even now we've done four non-significant risk studies; we're onto a fifth, and we're being challenged again, is it significant risk or non-significant risk? For a device, it's actually commercial already. So this is how challenging it can be.

And then from a reimbursement standpoint, obviously, we need to capture real-world data, NEST data, but we have to have reimbursement to do it. So next slide.

We have got a number of proposals from the AdvaMed working group, tax proposals, NIH proposals, FDA proposals, CMS proposals, and we think that these can maintain legal requirements for a demonstration of safety and efficacy but significantly

accelerating the funding and development. Next slide.

I'm not going to go through all of these. I'm going to just kind of pick one. The top one is one that I'm most interested in, and this is tax incentives for investment. Similar to the angel tax credits, we need to have something like this at the federal level to entice investors to do this. Next slide.

The FDA proposals, we have a lot of good FDA proposals. The one that I'm most interested in is having ped experts watching over the review process and making certain that we have a least burdensome approach. Next. Next slide.

From an NIH perspective, absolutely, the idea of NIH stepping in and providing leadership would be very helpful for identifying endpoints, surrogate endpoints, and adaptive designs. Next slide.

And then CMS, which maybe is the most important and the most problematic, we need coverage, we need coverage and payment during the trials, we need coverage once the devices are cleared or approved, and we have to have some form of reimbursement or relief to get some progress going to allow the devices to be used while we're collecting real-world data so we can see exactly how these devices work.

Thank you very much.

(Applause.)

DR. SILVERSTEIN: Thank you very much.

Our next talk will be on the use of real-world evidence using the National Evaluation System for health Technology, and our speaker is going to be Rachel Rath, who is the Deputy Director of the NEST Coordinating Center.

MS. RATH: It works. All right, so thank you, everyone. I'm happy to be here today. I get to take a few minutes and tell you a little bit about what NEST is. We've heard it mentioned a few times today, so now I'll back up a little bit and tell you a little bit about our

history and initiatives we have going on today, including some pediatric projects.

So for those of you who are maybe a little bit less aware, NEST was originally envisioned back in 2015 as a collaboration, a data network of collaborators, and was originally envisioned by a planning board, and in 2016, a grant was made from the FDA to the Medical Device Innovation Consortium to actually fund NEST.

Since that time, in 2017 we launched a multi-stakeholder governing committee; it includes all of the stakeholders you see there on the side of the slide, so clinician groups, patients, industry, regulators, payers are all at the table of our governing committee.

So far this year, we have launched initial studies called test cases in order to start testing our original data network. Our original data network launched just at the end of 2017, and I'll talk a little bit more about that in just a few moments. We've also launched a data quality subcommittee and a methods subcommittee.

As I just mentioned, we launched our initial data network of collaborators back at the end of 2017. The original data network includes 12 collaborators, the majority of which are based in health systems; however, they don't just have access to EHR data. They include data when it goes to public claims, private claims, PROs, and in some cases, pharmacy data as well. Two of these collaborators do also have UDI already implemented or a proven ability to implement it. This set of 12 collaborators represents over 150 hospitals, over 3,000 outpatient clinics, and nearly 470 million patient records.

In order to start testing the capabilities of our data network, we launched what we call test cases. This was an announcement that we put out at the end of 2017 asking manufacturers what questions did they want to see answered by the data network. So in this initial call that went out at the end of 2017, we had a few different goals. We wanted to test the ability of the data network to answer the questions that were important to manufacturers. We also wanted to test the ability of the original network collaborators to

actually capture that data and answer those questions. So we're very appreciative of the network collaborators and the industry partners who have been working with us really for the last 8 months now on these projects.

And today we have a portfolio that is still in development of eight different test cases. As you can see from the list here, these span the total product life cycle. We have a premarket test case, we have label expansions, we have postmarket, we even have one on clinical guidance, a range of products in areas including cardiovascular, orthopedics; we have a dermatology project, a vascular project, and a surgery project as well. These projects are still in the early stages, and they're still in development, and we hope to be making full announcements about this portfolio of projects in early fall.

I'm going to dive into two of these test cases now, which actually are focused on pediatric populations.

So the two test cases that are focusing here on pediatrics, oh, I skipped it, sorry. One of the orthopedic test cases, and this is a postmarket test case, this test case is focusing on one orthopedic device focused on craniofacial reconstruction, and it is a postmarket test case. Our second pediatric test case here is on topical skin adhesive, and this is a premarket test case. This test case is looking to try to determine the value proposition for this manufacturer to bring a product into the U.S. market that's currently approved in the EU.

So these are two examples of sort of a range of different projects, different test cases that can be answered and are under way in the data network now in order to help answer those questions that are important in the pediatric community.

In parallel to all of these, we need to make sure that the data being used by the network collaborators, the real-world data there, is of high standards. So we've recently launched a data quality subcommittee. We've also launched a method subcommittee to

really ensure the statistical methods of what that real-world data is being used for. So these two subcommittees were launched just about 6 weeks ago, actually summer is moving very quickly and these were selected through a public call. So these are multi-stakeholder groups. They represent industry, they represent health systems; there is some overlap with the network collaborators themselves, and there's also FDA representation on both of these subcommittees.

Both subcommittees are charged with creating standards. We're hoping that these subcommittees really build off the work that's already been done by IMDRF, by MDEpiNet, by PCORnet and other initiatives that have already done a great job developing standards to start with. We're hoping that the data quality subcommittee and the methods subcommittee have draft standards in place by the end of this year, so we're going to be getting them moving very quickly.

The next thing I wanted to note is that we actually have another call for test cases that's open right now. So what's important for us is that the questions are coming in from stakeholders in the ecosystem. So the test cases that we are implementing really come from you, so our data network is attempting to be responsive to the needs of the manufacturers, the health systems, in this case payers as well, and patient groups.

So we have two announcements that are currently open for NEST-funded projects. The first one is a general test case call. This is very similar to our first round of test cases and open to general concepts. The second announcement that we have open is for patient-generated data test cases, and these are test cases that must look at patient-generated data being used in those projects. And this announcement is also open to patient groups to submit their concepts as well. So both of these concepts are open now, and we'd love to see some pediatric questions coming in through the submission applications. Both are due in mid-September on the 19th.

That's a brief overview of NEST. We are looking very much to engage with the ecosystem. There are a lot of different opportunities. You can come talk to me, you can find us on the website; there are opportunities for engagement always posted on the website, and we are looking forward to helping answer the questions that are important to the pediatric population and each of your stakeholder groups.

(Applause.)

DR. SILVERSTEIN: Thank you very much, Rachel.

The next talk will be given by Dr. Randy Brockman. Advance this a little bit. And he is the Clinical Deputy Director in the Office of Device Evaluation in CDRH here at the FDA, and Randy's going to talk about the benefit-risk paradigm that he has helped develop here at the FDA.

DR. BROCKMAN: Thanks, Doug. So as Doug said, I'm Randy Brockman. I'm the Clinical Deputy in ODE, and over the last several years, one of my principal roles has been to help implement benefit-risk. After listening to Steve, it sounds like I've got a little bit more work to do.

(Laughter.)

MR. ANDERSON: Make your promise.

DR. BROCKMAN: So over the last 6 years, CDRH has issued a number of benefit-risk guidance documents. I'm not going to go through all of them. On this slide I list two. These deal with two of our most complex marketing applications, PMAs and de novos. One of the principal goals of the benefit-risk approach is to try to improve the consistency, predictability, and transparency of our review process, and this is something that we continue to work on.

So medical devices, as you all know, can be evaluated using both clinical and nonclinical test methods. On the slide I've listed a number of the nonclinical types of tests

that we often receive in support of marketing applications. We often get lots and lots of test reports.

Our benefit-risk assessment can be informed by both clinical and nonclinical data. As a clinician I tend to focus on the clinical data side. I've listed here a number of the types of information we can often get from the clinical evidence. This largely comes from the regulatory definition of valid scientific evidence, and it's pretty broad. As you can see, it ranges from what I've always considered to be the gold standard, randomized controlled trial, apparently, it's now called the dreaded randomized controlled trial as well.

(Laughter.)

DR. BROCKMAN: And it ranges all the way down to reports of significant human experience.

Well, how do we think about the clinical data? I think this is sort of the crux of the matter for me. Clinical judgment is critical. We have a number of review aids, and I'm going to talk a little bit about those. We have review aids, we have templates, a number of things to help our staff think about the data and process it, but none of that is intended to remove the judgment of our clinical experts.

In terms of the statistical analysis, it is important to us and it absolutely informs our benefit-risk determination. But the decisions we make aren't driven by p-values. So, for instance, failure to meet the primary endpoints of a study doesn't mean that it's the end. Of course, it works both ways. Meeting your primary endpoints doesn't guarantee approval; failing to meet your primary endpoints doesn't guarantee disapproval. We look at all of the information.

So we look at the totality of the evidence. We don't stop at the primary endpoints; we look at everything that we're provided. What we're really looking for is to see are there benefits to the device, and do those benefits outweigh the risks. And we pull in a number

of factors. I won't go through all of them, but I will touch on a few of them.

Along those lines, when we get a marketing application, one of the things a sponsor includes is a proposed indication for use. So if the data supports the proposed indication for use, if the benefits outweigh the risks, then we'll certainly work with the sponsor along those lines.

But sometimes the data doesn't support the proposed indication for use, and what we don't do or at least what we shouldn't do is just say no and send a negative decision letter. If the device provides benefits to patients and we think those benefits outweigh the risks, even if that's not for the indication as proposed by the sponsor but for a different or modified indication, then we should consider it and we should talk with the sponsor and see if that's acceptable to them.

As an example that I think would speak to this audience, if a sponsor developed a product for a given medical condition and they wanted to indicate it for the entire pediatric age range, when we look at the data it doesn't really support the entire pediatric age range, but it does support, for instance, the adolescent age range. Well, we should not just say no, and we should go back, talk with the sponsor, would you be willing to go there, and if they are, then we can work with them on it.

That's one of the goals that we have in mind with some updated benefit-risk tools that we're testing. The first tool we had was the benefit-risk worksheet, and it was certainly a step in the right direction, and it identified a number of factors and questions to consider, and it helped our staff focus on those issues. But it lacked a couple of things that we think are important. It didn't have a systematic way to turn that information into an appropriate benefit-risk assessment, it lacked decision support, and it didn't prompt our staff to think about an alternate use if the data didn't support the proposed use.

So right now we're working and testing a revised set of benefit-risk tools. The

original worksheet that came out in the benefit-risk PMA and de novo guidance did include this list of factors and questions to consider and we've continued to incorporate those. But that worksheet lacked decision support, and we think that that's pretty important, so the revised set of tools has a qualitative decision support, it's quantitative, and it also prompts staff to consider ultimate uses.

Patient preference information is important to the Center. We first rolled it out in our 2012 benefit-risk guidance, but we didn't talk much about how we would use it. Since then, a lot of work has gone into the area, including developing methodologies for how to acquire patient preference information that would serve as valid scientific evidence that we can use in our decisions. So since then we've finalized a patient preference information guidance and also updated our PMA and de novo guidance to better explain how we think that information could be used.

In the interest of time, I will skip that one. I did want to just give you a hypothetical example of how we might use patient preference information or, more to the point, how it might be useful to us.

So think about a life-threatening condition that, when associated with advanced symptoms, really has a negative impact on the patient's quality of life. A device is developed to treat that condition and it's a permanent implant. On testing, it improves symptoms but it increases mortality. That's not ideal. The right decision might be not to approve that.

But then think about a patient preference study. You can envision a study where patients are asked how would they view those benefits and those risks, what would be acceptable to them. You can imagine that a patient would probably say it depends on how much benefit is there and how much risk is there. It might also not be surprising to find out that it depends on the stage of disease. So patients with more advanced disease might be

willing to accept more risk for a given benefit or perhaps a lower benefit for a given risk.

Now, this isn't to say that we would view the data differently if there was a tiny benefit and an enormous mortality risk, but many times we struggle, we're having trouble figuring out where's the benefit-risk tradeoff that patients would be willing to accept, and in those cases, a patient preference study might be very helpful.

So I've tried to very quickly give you a high-level overview of how we view evidence, how we make our benefit-risk determinations. Hopefully, I've clarified things rather than confused you. But the bottom line is we're trying to make beneficial products available to patients, and after all, this is all about the patients, and that's our focus. So I will stop there. Thank you for your attention.

(Applause.)

DR. SILVERSTEIN: Thanks very much, Randy.

Our last talk is going to be on the Pediatric Extrapolation for Devices, I'll call it here the PEDs team. This is a team that was developed by Vasum and has involved many of the pediatricians in the Center for Devices, and Jackie Francis is going to talk to us about the novel approach to extrapolation. Jackie is a medical officer in the Office of Device Evaluation, a pediatrician in CDRH.

DR. FRANCIS: Okay, it works again. Okay, so I am, as Doug mentioned, here to talk about the PEDs team, which is, again, a novel approach to extrapolation in the Center. My objectives are to provide a brief overview of the extrapolation guidance which was created in 2016, well, finalized in 2016, to describe the PEDs team pilot and to provide an overview of the PEDs team consultations that have been conducted thus far.

So as we've talked about this morning, we know that there's a need for pediatric devices, but there's a lot of unmet need that needs to be addressed to the small sample sizes. You voted on that as well, so I might be a bit redundant on this slide. But the

extrapolation guidance itself proposes a framework to leverage the appropriate data for minimizing the risk to patients, to pediatric patients, while maximizing the access to medical devices indicated for pediatric patients. So we're hoping that this approach can stimulate the growth and the number of devices indicated and labeled for pediatric patients.

Okay, I'll briefly go over the regulatory background. Title III of FDAAA, which is the Pediatric Medical Device Safety and Improvement Act, authorizes the use of adult data to assist in the determination of pediatric effectiveness, and that was the foundation for the extrapolation guidance.

So extrapolation refers to the leveraging process where an indication in a new pediatric patient population can be supported by existing data from an already studied population, and that can be adults, that can be another pediatric subpopulation. And so when existing data are relevant to a pediatric indication and determined to be valid scientific evidence, which Brock already defined for me, thank you very much, it may be appropriate, then, to extrapolate such data for pediatric use.

So in the process of determining the appropriateness of pediatric extrapolation, there are three factors that we consider: similarity of the adult response or the population characteristics as it pertains to the intended pediatric subpopulation; the quality of the data such as the study design, bias use, data collection, endpoint evaluations; and also ensuring that there is reasonable assurance of safety and effectiveness or a probable benefit if there's an HDE as it relates to having valid scientific evidence.

So there are three possible decisions with regard to extrapolation: The first option would be the full extrapolation option where existing data can be used as a complete substitute for or as a substitute entirely for prospectively collected pediatric data; whereas the partial extrapolation will offer a combination approach where there may be some prospectively collected pediatric data, and that can be used with the existing data that will

be leveraged; and then the last option would be that extrapolation is not appropriate, and that would imply that the data are insufficient to meet the threshold of valid scientific evidence.

So inclusion of that extrapolated data, that data can be extrapolated, does not necessarily mean that the data are sufficient to support an approval decision. So if the data are seen, if the extrapolated data are appropriate and the data can be, then the data will be considered in conjunction with the totality of the evidence that was submitted, and that can either support or not support reasonable assurance of safety and effectiveness or probable benefit.

So with regard to the PEDs team pilot, this is a voluntary novel approach within the Center where we use a team of experts to discuss the appropriateness of extrapolation with regard to any application that we received a consultation for. And we believe that there is benefit to our internal teams, to sponsors externally as well, to having a centralized group of pediatricians and expert pediatric device evaluators who work together towards having a consistent and unified transparent approach to extrapolation.

So we aim to engage with the lead reviewers, and the lead reviewer would approach the pediatrics team with a consultation about whether or not extrapolation is appropriate. Then we would collaborate with that lead reviewer with regard to our PEDs team experts and discuss the appropriateness of extrapolation and therefore empower that team leader to go ahead with a recommendation to sponsors.

So the PEDs team, the volunteers, and I stress volunteers, they applied to join our group, they received division concurrence from their division leadership, and the applications were reviewed by Dr. Peiris and myself and Dr. Thompson, and we approved these applications for being a participant in the team. Dr. Thompson and myself are the PEDs team co-leaders. We have 14 voting members and 12 nonvoting junior members who

all have various levels of expertise in either pediatrics or pediatric medical device development. And the team consists of medical officers, statisticians, compliance staff, and again, just people who have some experience in pediatric device evaluation.

And as far as the actual consultation approach, if a consult was submitted to our team, then I would select one of the voting members and one of the nonvoting members to work together to be the lead representative for our consult, and they were selected based on their clinical expertise, their regulatory expertise, and also their workload because, again, this is a voluntary team and we have day jobs. So next slide.

So we would evaluate the proposed extrapolation approach for all application types that were submitted to us. We would make recommendations based on the majority of votes and provide an explanation for the majority perspectives and the minority perspectives. And we would clarify the options to achieve extrapolation if the information that was provided in the application was insufficient, and I'll talk more about that in a moment.

So with regard to the consultations that we've received within the Center, basically, we've received three applications that the team reviewed. One was a de novo application where we mostly unanimously agreed that partial extrapolation was the best approach. And the other de novo application, the team agreed that no extrapolation was appropriate, but we provided recommendations that might help the sponsor to achieve a possible extrapolation approach, if that was appropriate and if data were available. The last application was a pre-submission where the team was essentially torn. Some of us believed that partial extrapolation was appropriate, and some believed that full extrapolation was appropriate, and in that situation as well, we provided examples of how both approaches could be achieved.

And CDRH itself has also participated in the advising of other sponsors to achieve

extrapolation and on extrapolation approaches, and these are some of the applications that have been approved using extrapolation approaches, and I won't go into those.

But, in conclusion, the PEDs team is a novel and flexible approach to integrate expertise into all of the areas of pediatric medical device approval, and sponsors and FDA staff have been informed about this team as a useful resource. The PEDs team remains available for FDA consultations for any proposed extrapolation approach, and based on the review of the pilot, if the PEDs team continues to demonstrate improvement to or value to the Center's workflow, to the sponsors, and to the general approach to pediatric medical device development, we hope that our responsibilities will be increased. And I would always recommend that any sponsor that might be considering extrapolation approaches with regard to pediatric indications certainly submit a sub-Q application early and then we can be involved as early as possible.

Thank you.

(Applause.)

DR. SILVERSTEIN: Thank you very much.

And I think we heard from a variety of speakers, and so now is the time for a 10-minute question and answer discussion. If anybody has any questions, please come to the microphones in the front.

DR. SNYDER: Hi, how are you? Brian Snyder. So I sit on the NIH study section for tissue engineering and a lot of medical devices, and one of the talks talked about NIH and the role of NIH. The problem is that I'm the only pediatric orthopedic surgeon; in fact, I'm the only pediatric clinician on that study section, and of 30 people, there's only three other clinicians.

So the problem is that the devices and the tissue engineering approaches and things that we see are always going to be much more skewed towards things that affect the

general population, so just cancer and osteoarthritis and things like that. And the pediatric devices sort of will get a reasonable score, but there's nobody other than me and maybe, you know, one other person trying to advocate for that. So we're never going to get the basic science done because we lose the effect of how do you compare to heart disease and cancer.

DR. SILVERSTEIN: Well, I think it's a very provocative comment and that would be very interesting. I would open it up to the panel to see if you have any response. I bet Steve Anderson, I think it was you who mentioned the NIH, if I'm not correct, but maybe.

(Laughter.)

DR. SILVERSTEIN: Well, no. Actually, I thought that it was a very good important point that you brought up because it's an important element of what we do, and what you just mentioned is important, so maybe if you want to respond to that or anybody else does.

MR. ANDERSON: Well, you know, certainly we, on the ped working group at AdvaMed, we had a number of proposals and, you know, maybe one could argue we had too many, but we wanted to make sure that there were a number of things that were discussed in terms of possibilities. And I certainly understand that the resources available may not be there for some of these, and maybe we're going to have to find other funding sources and maybe Congress is going to have to help. I find it hard to believe CMS is going to just start throwing more money around, but you know, certainly the challenge there is not that different, though, than the challenge that we have within the companies; 99.9% of our resources are dedicated towards adults, too.

And so it's, you know, on both sides of the equation, the industry developers and clinical sponsors and the reviewers and regulators, we're all resource limited in this space because of the small numbers compared to what appear to be, you know, large or maybe more important adult populations.

DR. PEIRIS: Doug, if you don't mind. Brian, thank you once again for asking very provocative questions. This gets to the point that the Commissioner noted earlier regarding the fact that we want to ensure that appropriate expertise is available when we're discussing the pediatric-specific issues. I noticed that Alison Cernich from the NIH is standing right behind Matt there, and Matt, if you don't mind, Alison, I'll kick this over to you.

DR. CERNICH: So I think it's a well-appreciated point and not just for pediatrics but also devices, right? So devices are not as well understood at times, and I know that my colleagues and I at the NIH are trying to change that, especially at NIBIB and at NCATS. And so I'm from the Eunice Kennedy Shriver National Institute for Child Health and Human Development, and I also direct the National Center for Medical Rehabilitation Research; we're very interested in rehabilitation and assistive technology devices, and I think that the challenge is multiple.

Pediatric research is not just done at NICHD; they only do 18% of the pediatric research that's covered by all of NIH. So NICHD is now leading, through Diana Bianchi's efforts, a pediatric research consortium that is pulling together all of the institutes that invest in pediatric research and identifying needs. And so I think if you have, I know that AAP has been very involved in this as well, but I think this is something that needs to be brought to the forefront in terms of how do we advance this. And I know NICHD has funded a number of small business-initiated research fellows as well as RFAs on pediatric devices, especially in perinatology, and we have in pediatric devices for rehabilitation through NCMRR.

So we know it's a need, but I think the more that this community, working with FDA, working with NIH, can work with us, I'm sure that we can get to some productive solutions. So thank you, Vasum, for the time.

MR. BOCELL: We have an online question.

DR. SILVERSTEIN: I think we have a phone or an online question.

MR. BOCELL: Yes.

DR. SILVERSTEIN: So if you want to run with that.

MR. BOCELL: Yes, thank you. The question is what work is currently being done by the PEDs team in extrapolating data for use in in vitro diagnostic devices?

DR. FRANCIS: Actually, I don't hear anything. Is it working? Oh, okay. It's on, this is on. Okay, we haven't actually had any applications yet for in vitro diagnostic devices, but we're open. We just haven't had any yet.

DR. SILVERSTEIN: Yeah. And I think that one of the things that Vasum has really impressed upon us, and I think a lot of the pediatricians in the Center have adopted the viewpoint, is that we can't be passive, we have to be active, and that may sound like a slogan, but it really is true. In meetings I've had with companies where they don't seek a pediatric indication specifically, they're looking for adults, I will ask them are you seeking a pediatric indication; if you're thinking about it, let us know. If you haven't thought about it, let's talk about it. I think that if we play an active role in getting companies to think about pediatrics, then I have found many of them would then pursue.

Now, we understand that there are marketing issues that go with that and limitations, but I think that it's no longer a time when us at the FDA can take a back seat and just say, well, if they're looking for a pediatric indication, fine, because if they're not looking for it and they don't have an adult indication specified, it therefore includes pediatrics by default. If you don't mention an age, then it includes pediatrics. So I think it's best to get good data and then to have them seek a pediatric indication. Go ahead.

DR. MALTESE: Thanks. Thanks to the panel for preparing your remarks. It was a very interesting discussion. I'm Matt Maltese from Children's Hospital of Philadelphia. My

question is about this concept of valid scientific data. It's for everybody on the panel. I've worked with a few devices that have had publications that occur kind of outside the sponsor's purview but yet support the use of a device but haven't been deemed, even though they are peer reviewed, as not valid scientific data. For good reason. I guess my question is, is there a way to bring together the FDA community who makes determinations on valid scientific data and the journal publishing communities to either maybe have a set of guidelines or a stamp of approval or some other mechanism to prevent or at least mitigate this loss of resources that go to scientific studies that are published in the peer-reviewed literature, sometimes in luminary journals, but don't meet the quality standards or whatever standards for valid scientific data? Any thoughts on that?

DR. FRANCIS: So the challenge sometimes with some of the protocols when they are submitted, well, let me go back. For literature that may be submitted to support a clinical indication, the typical barrier is that the endpoints don't line up. I mean, it's hard to kind of make a general kind of example, but there may be specific indications claimed on the application that aren't quite going to be evaluated in a study just because a study may have totally different objectives, and the whole point of it, they may be evaluating different things in general.

So I don't know that it's necessarily that these studies are invalid or they're just not valid enough. It's that sometimes those endpoints don't line up, or sometimes the sample size, the patient populations don't line up, or sometimes there's just enough difference that it makes the data almost not poolable, which becomes a statistical thing that I'm not the expert on. But those are some of the things that feed into why we can't always use any readily available data to support a clinical application. And it's broad. It's difficult to really approach your question because there's a kabillion studies.

DR. MALTESE: Because it depends.

DR. FRANCIS: Right.

DR. MALTESE: Yeah.

DR. BROCKMAN: It depends, right; that's our favorite answer. That's only acceptable depending on what follows it, though, right?

DR. MALTESE: Yeah.

DR. BROCKMAN: So, you know, there may be a difference between was it valid scientific evidence and was it actually applicable to the application in front of us, and so maybe offline we could chat about that. It's an interesting idea, though, that you put on the table, but I will say that we use peer-reviewed literature not infrequently. So, you know, don't take from that, oh, peer-reviewed literature is not considered to be valid scientific evidence; that's certainly not the case. We can consider literature.

DR. MALTESE: Yeah. I'm not suggesting that. I think your point on the endpoints don't line up is the case that I observed. I also wonder if you've observed cases where you wish you had access to the original raw data, in which case you could maybe parse it, and if that was made to be a standard in publications as is the case for many journals now, that that would help. Have you observed a lot of that?

DR. FRANCIS: Well, as you mentioned, I don't think I've reviewed anything where we could actually get the raw data because they're proprietary authors
and (interrupted).

DR. MALTESE: I think that's changing in journals, and I'll stop. That's changing in journals now, that the raw data is becoming available.

DR. BROCKMAN: So what I can tell you is it's not an uncommon request, can we get the line item data?

DR. MALTESE: Yeah.

DR. BROCKMAN: So I think if that were available, it wouldn't hurt.

DR. MALTESE: Yeah, thanks. Thanks so much.

DR. SILVERSTEIN: I think that's a very informed question, and I think we have time for one more. James.

MR. BAUMBERGER: James Baumberger from the American Academy of Pediatrics. And thank you, Dr. Francis, for your presentation on the PEDs team. It sounds really exciting and a great model for when you have device companies who are interested in ensuring that their devices are labeled in pediatrics, that they can actually get some good technical assistance from you all.

My question goes to, I think, what Dr. Silverstein was just talking about, which is how do we engage the companies who aren't thinking about pediatrics but are going forward with an adult development program to start thinking about pediatric labeling early on as much as possible? Theoretically, there are lots of adult devices that could be eligible for pediatric extrapolation, but if they're not thinking about it because it's not in their business model, they're not going to be coming and asking you all for advice on it.

So it's great that, you know, folks like Dr. Silverstein are asking device companies to think about this, but how do we systematize this so that every time a device application comes in to FDA and someone is exclusively thinking about adults, how do we make sure that every such company is being asked about extrapolation so that FDA can provide them assistance and we can explore pediatric labeling?

DR. FRANCIS: Well, I think to start, the challenge might be that we get mostly involved in those questions during the sub-Q stage, and not everyone submits a sub-Q. And that would probably be the best time to approach any kind of question like that on the front end, particularly when we're sorting out, well, but again, we're still restricted because of the questions that are posed to us. We can offer some suggestions, but literally the layout of that is that we're supposed to be responding to the sponsor's questions.

We can be proactive; we can ask questions when we think it's appropriate and, you know, we might have to work within our cells to sort out how we can approach that. We don't quite have a unified approach, per se, with regard to all of pediatric approaches or indications throughout the Center. So, again, the PEDs team is kind of, if you have an extrapolation approach, you come to us, but we don't deal with everything.

And what else did you ask about? Oh, well, something else that we can do is with the annual reports, when we do review all of the pertinent information that's available and any readily available data that exists, and that's an opportunity as well, to discuss with sponsors whether or not they're pursuing anything that we found in the literature that might indicate pediatrics might be an appropriate approach if it's not being considered. But those are kind of what we have now.

MR. ANDERSON: You know, with incentives for investment, and if you had investors that met certain pediatric-specific criteria for investing, it could be self-fulfilling in many cases. Now, the companies have the investors and they have the resources, and right from the beginning they have the ability to focus on maybe smaller markets than just the adult market. So we'd like to think that the incentives could help take care of that.

DR. SILVERSTEIN: I think, also, I'm going to finish it up here. We have about a 15-minute break coming up, which has now become a 10-minute break, so run, don't walk. But it's a very important point and, you know, each individual reviewer here can say I'm going to do my part, but it's got to be systematic. And I think that we're going to talk tomorrow about the marketplace and some regulatory considerations, and I think that may address a little bit of how do we systematize what individuals might be incentivized to do here and to get that into a broader scope. So I hope that we can provide a little more of an answer for you tomorrow, then, I think, a couple of very good suggestions here, and I hope we can maybe take that a little bit further.

So we have about a 15-minute break, and like I said, we're about 10, so just to try to keep on track, and we'll see you all in a little bit. And thank you to our presenters.

(Off the record at 1:49 p.m.)

(On the record at 2:04 p.m.)

DR. SILVERSTEIN: Poll Question Number 6. So I'll give everybody a second to get their devices out.

(Pause.)

DR. SILVERSTEIN: Do you want to put the next poll question up, please? Okay, so we are on Poll Question Number 6. And I think after with the prior discussion, and I think in a little more we're going to be hearing about what types of data are considered real-world evidence: EHR, registry data, claims data, published literature, and all the above.

(Audience poll.)

DR. SILVERSTEIN: Whenever you see all the above, it's usually the right answer.

(Laughter.)

DR. SILVERSTEIN: Oh, you guys agree with me. I'm just saying generally. So I think we have most of the people here, and obviously, I think part of the point of this session is to make it very, very clear that there are lots of ways you can generate data and data that's generated in the real world, how it's used out in the real world. And so you can see that the vast majority of you believe that all of those could be considered real-world data that the FDA could use as part of assessing evidence.

So we're going to go to the next session, and we're going to start off with innovative trial designs, and we're going to start off with Martin Ho, who is the Director of Quantitative Innovation Program here in the Office of Surveillance and Biometrics in CDRH at FDA, and Martin is going to talk about going beyond the randomized clinical trial.

DR. HO: Good afternoon, everyone. My name is Martin Ho. I am a statistician by

trade, so therefore, you know how difficult it is for me to talk about anything other than randomized clinical trials.

(Laughter.)

DR. HO: But I wanted to emphasize how important the patient is for our Center. Here we have the patients in our Center's vision statement first, which is patients in the U.S. have access to high quality, safe, and effective medical devices of public health importance, first in the world. I'm putting this slide first, not only because the Center Director asked us to put it first in the slide deck to remind us of our mission, but more importantly, I think, by thinking about patients, it really helps us to provide a focus across the expertise and technicalities on how to provide multidisciplinary solutions to a problem that's atypical and is badly needed to be addressed, such as the pediatric medical devices.

So as you may have known about this pretty well, there are challenges of conducting randomized clinical trials in pediatric patients. Compared to adults, they are harder to recruit, the trial may be longer, and also they may need to include multiple subgroups that are heterogeneously different. These are all, you know, well-known facts. However, by thinking about patients in this specific case, these pediatric patients, our Center has provided at least two other regulatory pathways to tackle that issue.

Jacqueline may have talked a little bit about using the existing data extrapolation to tackle this issue by borrowing information from adult data or other existing data to supplement their clinical trials data. And also in the previous session, we talked a little bit about what is real-world evidence. And since we have touched on those two issues, perhaps let me take a little bit, you know, deeper dive in on those two topics.

So we understand that the pediatrics, you know, extrapolating and assessing data for pediatric use are focusing on identifying relevant and valid scientific data for us to borrow straight from this information and to design a prospective study to address that. So, in

other words, here, although we have been talking about existing data, that means we are using existing data or retrospective data, but the technology and statistics actually allow us to design a prospective study with supplements from existing data.

So when we are just looking at the data, when we are looking at the data quality and relevance and the similarity of response to interventions, these are the concerns that Jackie had mentioned. But one thing that I want to emphasize is that in these cases we usually think about them on a case-by-case basis. In other words, we don't actually have a one-size-fits-all solution. So that's why I think Vasum and Doug have been, and Jacqueline has been working so hard, is because unlike other devices, they are paying extra attention to see how we can best leverage the existing information to make the clinical study feasible.

So the decision categories here are listed as three categories. I wouldn't repeat that, as Jacqueline may have mentioned that already.

So this is not an eye exam. I didn't mean to ask you to read them, but I just want to show this to help us to appreciate how much thought has been put into this process of Vasum and his team working together and trying to evaluate, you know, first about the relevance and then about different factors to see how we can best leverage existing data.

So now we jump to the next topic, which is real-world evidence. And we know that, you know, real-world evidence certainly has some benefit, which is where the rubber meets the road, and we can show the real-world effectiveness of the devices, but at the same time they are not in a controlled situation. So, in other words, there are bias and confounders that require to be mitigated, and also different providers may have different workflows and practices that need to be taken into consideration. Something difficult doesn't mean that we shouldn't consider them.

So here we are talking about two different concepts, use the real-world data, use the data that is related to patients, you know, collected routinely from a variety of sources, and

then the evidence is the result of analysis that are carefully designed and conducted in order to support certain very specific regulatory purpose. So, in other words, it's a three-step process. We first need to identify the sources of RWE, we have to carefully plan for analysis, and then keeping in mind what specific use of real-world evidence generated as a result to help us address the regulatory questions.

So in the previous session you also heard about NEST, and yes, it has just taken off, and here is, I think, a brand new concept because for us, we are no longer satisfied with just living with existing data, but rather we would like to create an organic network with people who are knee deep in the data that they have been using and living with so that we can generate an optimal result in a very cost-effective manner.

So in terms of real-world evidence, our Center has been using it to inform various device, you know, decisions for both premarket and postmarket. For premarket, we have been using that, the real-world evidence, we are using the off-label real-world evidence to expand the labels. We are also using that to inform our pivotal study design to make the decision shorter and earlier. And for postmarket, we are also using them to satisfy some of the postmarket surveillance requirements.

So, in sum, I would like to say that we are very happy to see all of you being here to work with us to help bring forward the solutions for pediatric patients using medical devices. Although, you know, RCT has been more resources and time demanding, but that doesn't mean that we cannot do anything about it. In contrast, we have provided a list to other regulatory pathways to tackle that question.

And, more importantly, I also wanted to add in another component that I am personally responsible for, which is the patient-reported outcomes. Even though we have been talking about different types of, you know, evidence generation, but a lot of times we measure a patient in 20 different ways but we forgot to ask them, how do they feel?

But imagine a world that when we have someone provide us with questions that have been tested across wide varieties of patients, and then they would be, you know, proven to be understandable to those patients, and their responses can provide some of the meaningful signals to help us better manage their conditions, I think I would take that. So, therefore, we are working very hard to develop, you know, new types of patient-reported outcomes that are specific for pediatric populations.

So thank you very much.

(Applause.)

DR. SILVERSTEIN: So as you could see, Martin wears a lot of different hats here, so thank you very much.

Our next talk will be Pamela Haworth, who is going to give us an industry case example for novel trial design, the MiniMed 670, and Pamela Haworth is the Clinical Research Director in Program Management for Diabetes at Medtronic.

MS. HAWORTH: Thank you. Thank you for the opportunity to share our experience with a pediatric device trial design and collaboration with the FDA.

So the MiniMed 670G is indicated for patients 7 and older. In September 2016 it was approved for 14 and older, and just this June we got the pediatric indication.

So what is Type 1 diabetes? This is a chronic condition. It doesn't go away; there are no vacations. It is actually an autoimmune disease where the body's own immune system attacks insulin-producing cells in the pancreas leading to zero production of insulin. One in 20 people will be diagnosed with Type 1 diabetes, and usually they're diagnosed when they're younger than 20 years of age. And until the discovery of insulin in 1921, this was considered a death sentence.

So what happens when we don't have insulin? Oh, thank you. What happens when we don't have insulin? Then the insulin really helps the glucose enter the cells and uses

glucose's energy for all of the cells in your body. So as the blood glucose increases, so does your insulin in order to combat the glucose. When your blood glucose decreases, your insulin decreases.

Now, just a show of hands, who thinks here that diabetes leads to heart disease, neuropathy, nephropathy, eye damage, foot damage, and skin and mouth conditions?

(Show of hands.)

MS. HAWORTH: You are wrong. So uncontrolled diabetes can lead to all of these conditions.

So what is the vision here? The vision is to really help the patient control their diabetes. And this just can't be a pump that just secretes stuff. You have to have different components within that pump. One of them is continuous glucose monitoring so you know what your sensor glucose is, the other one is insulin delivery, and the third one is a data review so that you can manage your diabetes.

So the MiniMed 670G system with SmartGuard delivers basal insulin every 5 minutes using a hybrid closed-loop algorithm. Several components are actually part of this system to ensure that two levels of automated insulin delivery are done. First, there are two levels; one of them is manual mode. Manual mode encompasses a couple of the things that our previous pumps encompassed, which is suspending the insulin on a low blood glucose or suspending the insulin before low, and also providing basal insulin delivery. In auto mode, the pump adjusts basal insulin every 5 minutes based on continuous glucose monitoring to keep it in target range.

So, on the right-hand side, you need the sensor and the transmitter to provide sensor glucose to the pump. And then on the left side, you have your meter. Your meter is needed for calibration of the system. And the CareLink system, actually, when your pump is uploaded, you're able to take a look at all of your data based on blood glucose, insulin

delivery, insulin usage. You do need to go into manual mode first. This trains the algorithm within the pump on the insulin use, and the algorithm adapts multiple parameters daily from the last 6 days.

So, in auto mode, it has an adaptive basal rate change, and the nighttime glucose and insulin rates primarily are functioning in closed loop because you have less interference with other parameters such as meals, exercise, stress, illness.

So what is so novel about our design? Actually, our last slide is about collaboration; that is really the novel design. Here we have a single-arm, nonrandomized study. Both for the adult indication and the pediatric indication, they have very similar designs. Again, nonrandomized, one-arm safety study.

So, after screening, patients are trained and their caregivers are trained on the devices and diabetes management, including treatment of hypoglycemia or hyperglycemia, and then to do their blood sugar readings with their blood glucose meter.

The first day of their sensor wear, they are doing a frequent sample testing day, 12 hours of frequent sample testing for 7- to 13-year-olds. This is to test the "suspend before low" feature in the pump. We want to make sure that we challenge the kids; there's a hypoglycemic challenge to make sure that that part of the system works.

Then they go through a run-in period where they get to know the system. It allows the patient to become familiar with all of the study devices. And once they finished the run-in period, they went into a 3-month at-home period. Part of that period was actually in a hotel. We had 6 days and 5 nights with kids, their caregivers, and the clinical study site personnel. They had daily activities where they had 4 or more hours of exercise, and they could pretty much eat what they wanted, which was very cool for them. And then there was one frequent sample test day as well. Every 60 minutes their blood sugar was tested during the day and every 30 minutes at night. This was really to ensure the effectiveness

during the day and at night.

So what are the results? They were really great. We had 105 patients complete the trial, 7- to 13-year-olds, the average age was 10.8, and their diagnosis of diabetes was about 5.6 years. We had 10,600 patient-days data, and what we found using CareLink data, that the sensor was worn about 95% of the time, which is kind of unheard of with some of our previous designs, and auto mode 80% of the time, which means that they actually saw a lot of time spent in range for their blood glucose.

A1c is a marker; it's a lab marker that shows you, over the last 3 months, how much your blood sugar was high or low. And for pediatric or for adolescents, we want to keep it at about 7.5%. But the baseline here was 7.9, and the A1c was decreased to 7.5 in just 3 months. And subjects with A1c less than 7.5% in the run-in were 36% and during the study were 51%. And these results were similar to the adult results. So we saw effectiveness for both SmartGuard and the closed-loop automated insulin delivery.

There was also recent real-world data MiniMed 670G system posters and presentations at ATTD and ADA, which shows the results of de-identified data uploaded voluntarily from commercial use, and we found 541 patients between the ages of 7 and 13, and it wasn't indicated for that. So we know that these patients are using it. Now we've got the labeling for it.

So what are some of the pillars of the clinical approach to safety and for this clinical study? So in terms of data collection, we had dedicated training on the safety of all the sites, validated data management system, robust monitoring, safety review by our medical affairs department on a continuous basis, validation of system performance using a reference which is called i-STAT or YSI, and incremental system improvements.

What we also had in this clinical study was a data monitoring committee, and this comprised of endocrine experts, including pediatric endocrinologists and independent

external biostatistician. What they did is they adjudicated the serious and glycemic events such as SAEs, diabetic ketoacidosis, severe hypoglycemia, and severe hyperglycemia. They reviewed the overall tracking and trending; they reviewed anything for stopping rules.

And then what we also did was an enrollment of the younger subjects. We currently have 2- to 6-year-olds in this study. We actually just finished enrollment, and we should be done with the study by December. So we gated the enrollment of the younger kids with the older kids.

The user experience: We had onsite diabetes education, there was a help line available to anybody who needs assistance, we had marketing questionnaires, and we also had very close communication with our pediatric endocrinologists at our site and made sure that we shared best practices. And, above all, we had an expanded use of the devices based on requests to the FDA. So the patients actually called the FDA and said we don't want to give this up, and so we allowed them to stay on the device after the study period.

And, again, I really want to thank the FDA and really acknowledge that our collaboration is what made this so successful because there are various devices and various algorithms within our system, and we had to do a lot of studies, feasibility, sensor accuracy, safety, and we do have a postmarket commitment. But it was the constant engagement working with the FDA in terms of monthly meetings to discuss update, strategy, and timeline and, to gain continued alignment with the FDA about our study design and the results. And, in return, FDA questions were always answered in a very timely, and sometimes within a day, manner in order to keep them engaged. And what happened here was accelerated approval for the adult indication, we had about 3 months from submission to approval, and with the peds, about 5 months with this nonrandomized trial that basically looked at safety.

So thank you very much for your time.

(Applause.)

DR. SILVERSTEIN: Thank you very much. A lot of detail in there, lots to chew on.

Our next talk will be Leonardo Angelone. He's a research biomedical engineer in the Office of Science and Engineering Laboratories (OSEL) in CDRH at the FDA, and Leonardo is going to be talking about study designs using modeling and simulation.

DR. ANGELONE: Good afternoon. I'm part of the Office of Science and Engineering Laboratories within the Center of Devices and Radiological Health. I don't know how many of you are familiar with the Office of Science. We do research, yes, that's one, and that's about right percentage. We do research; we publish papers. I strongly believe peer review papers are scientific valid evidence, maybe not sufficient, but they are. We're about 150 staff members plus post-docs and students in different areas. And we work with the Center really to support the other offices and the review programs. We work with outside Center. And the goal is to really provide patients access to a medical device, not just to have them approved but while ultimately the patient will be able to use them.

One message that I would like to convey today is when we think about models, and we heard real-world evidence, I will introduce the concept of digital evidence, and we think about clinical trials, animal testing, bench testing, and then we think about computational models. Well, computational models, they're a bunch of nice images of fake, not really science, we believe in clinical trials. But then we take the plane, we use the cell phone, and we never really, I mean, we take the plane, and we don't have a panic attack; we have confidence that the plane will bring us where we are going. What if I tell you, well, that plane has been built using computational models in addition to other tests. We take the car to go to work; again, we have bench test, we have phantoms, they're used, but also computational models.

Is animal testing, testing done on a dog, as close to reality than a computational

model that is being validated extensively in a series of data that have been taken from the patient MRI data and build the model and do the testing? Or they're all different type of tools that complement each other, in providing evidence in support of safety and effectiveness of the device? And if we start to see computational models as part of those tools, just like clinical trial bench testing, animal testing, then progress can be made.

And today I wanted to just briefly discuss one of the success story, which is the ability of having MRI and allowing patients with medical device access to MR. As you may be familiar with MRIs, one of the diagnostic tools, they're really most used in the clinical community with about 35 million scans in the U.S. per year. We have cleared MR systems for 1.5 T. Last year we have cleared 7 Tesla MRI system. And, really, there is an increasing number of uses.

Now, there are a lot of patients with devices, whether those are fully implanted devices, stents, orthopedics, so-called passive devices so no electronic components, whether they are patients with pacemakers, so neurostimulator implanted, cochlear implants, pediatric population, partially implanted devices or externals. All of those have a specific indication. The device can be fully safe. The patient can go and be exposed to MR without any problem, the patient may never be exposed to MR, or the patient can be exposed to MR within specific conditions.

The work we do to establish safety of patients is really a collaboration effort. This was mentioned before. Not by chance, collaborative communities, one of the priorities of our Center, and the work could not be done unless we interactively engage with different stakeholders in industry, in academia, and really with the healthcare providers, and that is our everyday job.

The example, again, going back in 2009, that's when I joined FDA, and back then there was no patients with pacemakers could have MR on MR exam; there was complete

exclusion. It was a poor contraindication. That was the year, again, I joined FDA, I started to be actually involved; this was one of the first cases where I was involved as a subject matter expert, and ultimately in 2011, the FDA approved the Medtronic Revo pacemaker, which was the first pacemaker with MR labeling. Why I'm bringing back is because in that case, computational models were used in the regulatory submissions, and as was reported by our Center Director, Dr. Jeff Shuren, and Owen Faris, which back then was the leader of the submission, now he's the Director of Clinical Trials, really, we can use computational model as part of evidence for assessing safety of devices.

Again, when we talk about computational model, we're not talking about a bunch of simulations, three or four, and nice images and color images. We're talking about an extensive, extensive study; they are based on real-world data, MRI data of patients. We build computational anatomic models, and then those data are tested against experimental data.

So I am showing a slide from Medtronic, actually one of their computational modeling framework. You see that there is a computational model, this is an animal study, a pig model, and then on the side, on your left-hand side, there is images of pigs. So the models were tested against and validated against physical data. And so the overall framework was then validated and was validated for a specific context of use, which is can we use the model to evaluate safety of a human body wearing a pacemaker into the MRI? And I'll show later if this can be expanded to pediatric population. Sure, it depends on what are the models you are going to use.

Another example, this is from Stryker. Again, computational models being used for safety of orthopedic implants.

And one more case. This is collaboration we're doing with InSilico Trials company in Europe, and Ansys. We're working building a cloud-based system where we develop

computational models we share, openly share with the community; so as said, this can be used as part of evidence, the evaluation of safety in this case, safety of passive implanted medical device. Again, it's a collaboration that we do. You have several tools that can be used that results in another program that has been started a few years ago by our Center, the medical device development tool. The idea is you can have tools; they are evaluated for a specific context of use and then used in that application. They are evaluated once and for all. And then different companies, if you have a tool that is establishing safety of any orthopedic implant and you saw that that platform has been validated for that context of use, then several type of orthopedic implants can use the same tool.

How then you go to pediatric application? I'm showing this is one of the series of computational model, anatomic model; they are being developed again by the FDA in collaboration with IT'IS Foundation about 10 years ago. Incidentally, this work was actually funded by cell phone, Mobile Manufacturers Forum. And, again, it's important to collaborate not only within the medical device community but to see what work has been done in other areas.

So these models were developed in the area of cell phones; we're looking at the same type of endpoint, radio frequency, interaction with the human body. Anatomical models were developed. First there were four of them, it was the Virtual Family, and then this was extended. You see this includes pediatric model and different ages, 5, 6, 8 years old as well as, of course, adult model and elderly model. And so you can generate a framework that then will evaluate the safety of a neurostimulator or a pacemaker by using this data. You may validate that.

And you can also build 3-D printer model. There was a question before about 3-D printing. This is an example of the vessel structure taken by the model, 3-D printed, and this is a bench test that can be used. Then you have a combination computational model

and physical evidence.

We're again working, I mentioned before, we work with the community, but this collaboration done with Mass General. This is a human head model. The data were from an adult. Can this be applied for evaluation of safety for a pediatric model? It depends, of course, but it depends also on what are the specific characteristics. If the size and the weight and the specific configuration of this model can represent a pediatric patient 15 or 18 years old, then it's something that can be used. And, again, this is models; they are freely available.

Last time, we're also continuing to collaborate, we are organizing a conference next year in collaboration with the Biomedical Engineering Society here in the D.C. area. You are all welcome to join. The discussion is really how models can be used for developing a medical device, and we have different areas, so all welcome to come. If you have any questions, feel free to contact me.

Thank you for your time.

(Applause.)

DR. SILVERSTEIN: And our last talk of this session will be an industry case example of Jarvik Heart. Tim Baldwin is the Deputy Chief of the Advanced Technologies and Surgery Branch at the NILB [sic].

DR. BALDWIN: Thank you, Doug. So I have nothing to disclose. I usually start with a disclosure slide here, except that I am serving a part-time detail as a reviewer here in the Circulatory Support Branch in the Division of Cardiovascular Devices at CDRH, and also my other disclosure is that the real experts on what I'm going to present on were not available, so it fell to me.

(Laughter.)

DR. BALDWIN: So for the past 14 years, I've been the program officer for two

programs that develop and clinically evaluate mechanical circulatory support devices for small pediatric heart failure patients. Only one device, the Jarvik 2015 VAD, has made it this far and is poised to be in a clinical study, the PumpKIN study, which was mentioned earlier by Dr. Lund, later this year. I'm going to tell you a very brief story of how modeling simulation reviews have developed this device.

I need to start with its predecessor, the infant Jarvik 2000 VAD. The Jarvik VADs are rotary blood pumps that work like large turbine pumps and spin at about 10- to 20,000 rpms, revolutions per minute. The infant Jarvik 2000 VAD was designed and developed using various engineering methods and principles by the staff at Jarvik Heart, who makes the device. This included a great deal of building and testing prototypes and refining the design. Unfortunately, however, 4 years ago, when nearing the anticipated end of the development of the program, we found that there was a significant problem with hemolysis with the device.

There were concerted efforts which resulted in a redesign. The normalized index of hemolysis or NIH, which is a measure using standardized in vitro testing, was reduced by over an order of magnitude to less than 0.1 g/100 L. I'm going to tell you how this was achieved and the role modeling simulation had in it. Being from a federal agency, the first thing I naturally did was form a task force.

(Laughter.)

DR. BALDWIN: The goal was to modify the device to reduce hemolysis levels to an acceptable level, which we chose as 0.1 g/100 L, while minimizing the changes to the pump, and we decided were going to do this using CFD, computational fluid dynamics, and in vitro testing. The first thing that the team did was try to determine what was causing the hemolysis because if we could identify the source, that would direct what design changes needed to be made. We looked at various potential causes and found none that specifically

could be attributed to the problem, although we did find it could be reduced by about half by smoothing the blade tips in the device, but this really wasn't enough. As a result, the team went back to the drawing board and applied some basic engineering sense to address it. Based on some initial work, the decision was made to slow the speed of the pump down. To keep the same pump capacity, though, this meant increasing the size of the pump.

We looked at two designs, two designs were pursued, one by Dr. Wu, who was running computational fluid dynamics simulations and had great experience with these types of pumps, and one by Jarvik Heart, who had another design that they thought would work. We looked at doing virtual modifications were made and prototypes would be built and contenders would be built to characterize hemolysis and see how the results compared to Dr. Wu's analyses.

Surface measures of the final designs for the CFD analysis are found here. I'm not going to go into the details of the designs and differences in there, in these; rather, I'm going to focus on the differences and results found in the CFD analysis.

This shows the results of a CFD simulation with fluid velocity vectors, which anyone who has seen a CFD presentation before have probably seen something similar to this. Note that the vectors are color scaled by localized normalized index of hemolysis, which reflects the level of local red blood cell damage by device. Also note that the scales are a little bit different between the two devices, the two images. The results, though, clearly indicated that the Jarvik 2015 design results in a lower hemolysis in the bloodstream.

This type of analysis was also done for wall fluid stresses on the surface of the pump. The results are shown here. While the Jarvik 2015 appears to have similar or maybe even a little bit higher levels, the scaling is also different, and there really is very little difference in this one.

Dr. Wu also calculated an estimated overall normalized index of hemolysis and how

it accumulated over the length of the device for each of the devices and compared them, as shown in this slide. Here it shows the NIH of the Jarvik 2015 as about half that of the alternative design. At this point, after the CFD analyses were completed, prototypes were based on the analyzed designs were fabricated and tested. The results reflected what Dr. Wu had predicted, and more importantly, the NIH values were vastly improved and were close to our goal of being less than 0.1. Further refinements resulted in the lowering of the hemolysis levels further, as I showed in the results earlier when I started the presentation. Additional analyses of the CFD data reveal good agreement with the in vitro hydrodynamic data as well as insights into the expected efficiency and power requirements of the Jarvik 2015 device when in operation.

This slide shows a comparison of the Jarvik 2015 to its predecessor. I just want to point out that the dimensions necessarily increased, as we expected, to address the hemolysis issue, so it increased from about the size of a AAA battery to the size of a AA battery. An upside of the larger size, though, of the redesign was that the Jarvik 2015's output was over twice as much as the infant Jarvik 2000, meaning that it could be used in larger children with greater cardiac support requirements.

Of course, we didn't end there. We next did a GLP study, GLP animal study, and these were performed at Texas Heart Institute under the direction of Dr. Iki Adachi at Texas Children's Hospital. We found that the results were quite good; there was no pump-related deaths, only minimal hemolysis, and the surviving animals were all in good health.

So, in summary, CFD and in vitro testing were instrumental in the redesign of the device that resulted in the Jarvik 2015 VAD, and while larger, it has a much lower hemolysis profile, which was our goal, and high flow capacity, higher flow capacity. We took the data, it was submitted to the FDA before I came here, by the way, and an IDE was approved for the NHLBI-sponsored pumps for kids, infants, and neonates, or PumpKIN randomized

control trial for the Jarvik 2015. However, as Dr. Ho pointed out, there are problems with getting randomized controlled trials done, and we experienced that. So instead of doing an RCT with the device, we decided, instead, to do a feasibility study. The IDE for that was approved by the FDA in this past March, and the first implant is expected later this year.

I just want to end on a positive note, another positive note. The first implant of the device actually occurred in February of this year. It was outside the U.S. in the Vatican City in February. It was in a young girl, and she's been on the device now for 6 months and is awaiting a heart donor for a transplant. So it's been a big year, and it could end with being a really big year if we can start this study.

That's why I give special thanks to a few people who have really contributed to the work to get here and especially Jingchun Wu at Advance Design Optimization who did all the CFD work. I mentioned Dr. Adachi before and also Dr. Jarvik and Jarvik Heart, who has been instrumental in making the device and getting it to where it is. And I also want to thank the PumpKIN trial leadership, including Chris Almond, who's in the audience here, and all the work that they're doing to get the trial under way. Thank you.

(Applause.)

DR. SILVERSTEIN: Okay, thank you very much to the speakers. Tim, I apologize; I got tongue tied. NIH, NHLBI, I got a little bit tongue tied and I combined them, so I apologize about that.

So, we have about 7 to 10 minutes for questions and answers, and I think there were a couple of people who had questions during the last session; you're free to come forward and ask those questions now. Or if anybody else has any questions.

(Pause.)

DR. SILVERSTEIN: Or comments.

DR. SNYDER: Brian Snyder, Boston Children's. So, I have a question. One of the

things we've had in orthopedics is certain devices that we've adapted for off-label use that have actually become the clinical standard. The problem then is trying to study we end up doing an end-around, doing a retrospective analysis. It would be better to actually try to look at that data in real time. The problem is trying to get it through an IRB to be able to study it, and it becomes a sort of Catch-22.

And my question is, in the talks talking about real-world data, is there a mechanism, if we put together a consortium of the places that are doing sort of these innovative techniques, to be able to either have an IDE for the entering of data on a non-labeled device, because the IRBs won't let us study it. Is there a way, in other words, because we're trying to collect data on a non-approved device, and currently, the IRBs at least, many of the IRBs at the big academic institutions don't look at that, so you have to do this end-around to do a retrospective chart review as opposed to really being able to study it the way that your real-world data is seeming like to be able to look at it in real time and compare. How can we try to study these patients, and what's the approval, is there like an IDE that we would get for the data entry?

DR. HO: I think our Center's approach has been just as you said, form a consortium and develop a registry network, so to speak, and then conduct our prospective studies, as we know that we are collecting information, we would be collecting information that are high quality and allow us to use that to inform, you know, to inform the regulatory decisions.

But as to your questions about the individual IRBs are not, you know, don't feel comfortable approving a study for retrospective chart review, for that, I don't have any specific answer to that. I feel your pain, though.

(Laughter.)

DR. HO: Also, I sit on the FDA's IRB, so I understand what you're talking about, but at

the same time, I think setting up a consortium and conduct a prospective study can be a way to go.

DR. SILVERSTEIN: Vasum.

DR. PEIRIS: Thanks, Doug. I just want to say that we're cognizant of the issues and the concerns that come up with IRBs and especially when they're asked to approve off-label use of devices for studying. We are very thoughtful about developing systems and facilitating access to data that can help generate evidence for enhanced labeling. I just want to let you know it's a topic that we're aware of, it is a topic that we are attempting to address, but maybe the primary issue is helping educate IRBs regarding their role and perhaps clarifying the FDA's oversight, and if there's any questions or concerns, they're more than happy to contact us.

DR. SILVERSTEIN: Yeah, I'm going to jump in on that a little bit, too. I think that we have gotten comments from companies and investigators that the IRBs are very, they have their ears tuned very closely to what the FDA says, and we're aware of that. And so sometimes it might help if you, you're certainly open, without your IRB, to come in here and have what we call a pre-submission meeting, we call it a Q-Submission, discuss what you want to do, and then based on those discussions, I'm wondering if you could take it back to your IRB and say we discussed this with the FDA, this is the kind of data they want, we're going to have to do a prospective study, but it's an off-label device so therefore we have to go through an IDE.

And I think if you can maybe start with that process, it's maybe a fruitful way to get the information you want and provide that to your IRB, and maybe they'll think about it a little bit differently. I'm hoping that's the case, but I don't want to lead you down the wrong path, but at least, at the very least, it allows you to have an interaction with us to try to find out what kind of information we would want.

Go ahead, please.

DR. STRASBURGER: Janette Strasburger from Milwaukee, Children's Milwaukee. I just had a question for Dr. Baldwin. What was the rationale for going back to a feasibility study after starting off with something that appears to be ready for a randomized clinical trial? Could you maybe discuss the rationale for going back to a feasibility study there?

DR. BALDWIN: Well, there's the big problem was equipoise. And also reimbursement. As we got deeper into it, we felt there were some that thought, well, we have a device, the Berlin Heart, that was randomized to that we used, you know, we were reimbursed for, and it's going to be hard to get reimbursed, we're not sure whether we will, and some thought it's been proven and here's a device we were taking a risk on and there wasn't, and so some people thought, well, I really hope that my kids get randomized to the Berlin Heart, where others thought, I even had a call from someone, I won't mention who, said if I randomize it, can I get randomized to the Jarvik device? I said, no, that is not the way randomization works.

(Laughter.)

DR. STRASBURGER: Thank you.

DR. BALDWIN: There were other issues, but that was the big one.

DR. STRASBURGER: Thank you.

MR. MATLIS: Hi, I'm Dan Matlis with Axendia, and one of the challenges that we see in the industry is not the lack of data; there's a lot of availability of data. The challenge is access to that data and especially as it relates to pediatric devices. Can we harness the data that is available so that we can build models to actually simulate virtual human models? I know one of the big concerns we see, I was talking to an executive, and he said we want to end up with a digital twin, but we end up with a digital mutant instead. So how can we harness all this in order to create virtual human models?

DR. ANGELONE: This is actually the effort we are working in how we can access all the data out there. We have done some work also for, again, for the MRI example, we've done some work internal where we looked at all the data submitted to the FDA, we mined those data, 510(k) and PMA-approved data, we anonymized them and made them available, and we're using them now to establish a new standard and for models.

And it really is a community effort. The example I show on the head model, that required a group in Zurich to collect the data, a group in Boston to evaluate them, a group here to then do the segmentation and then do two or three rounds. So that is really a communal effort. Part of it has to do with competitive or precompetitive space, so one could argue that now the MR labeling for 1.5 is what's considered precompetitive. If we look too high, we are in very much competitive space. So that is also something that, it will eventually, and we say, okay, is this really something that we can share; maybe major companies are looking at small device manufacturers, so yeah.

MR. MATLIS: Is there an opportunity for the FDA to actually spearhead similar to what you've done with the living heart model and building that?

DR. ANGELONE: There are several efforts in like our office where we're leading efforts in developing models and share, and the conference we mentioned, that's where we can work together, maybe develop, as I mentioned, on a medical device development tool, and it's a win/win for us; we don't need to review always the same type of data, and others don't need to focus in part that is not even part of their device.

MR. MATLIS: Thank you.

DR. ANGELONE: Sure.

DR. ESPINOZA: Hi, Juan Espinoza, Children's Hospital Los Angeles. I had a question for Dr. Haworth from Medtronic. I was wondering if you could talk about some of the lessons learned or your experience sort of in that period in 2017 to 2018 when CGM devices

were not being reimbursed and patients were accessing their data through either app portals or web portals. And so there seemed to be a disconnect between CMS, FDA, providers, and how patients actually wanted to use their device, and I'd love to, if anybody from the FDA would like to comment on sort of lessons learned from that process in terms of the disconnect between what CMS was doing and what this organization had done in terms of approving those devices.

DR. HAWORTH: I'm not really sure I know how to answer that; maybe an FDA person can help. In terms of accessing their data, we do have CareLink so that they can access their data, and we actually now have a new device so they can see it on their phone. So, you know, if they want to see it, they'll see it. It's out there and other device companies have it as well.

DR. SILVERSTEIN: Go ahead.

DR. ALMOND: Chris Almond from Stanford University. I just wanted to tack onto Tim's comment about enrollment. I think this is such a great conference because it's looking at all of these different barriers, and some of those relate to regulation or trial design, but one of the key ones, I think, really is enrollment in trials. And I've forgotten who mentioned it earlier today, but this is a critical issue; we can't really execute trials and get the data if we can't enroll, and as pediatricians, we're incredibly risk adverse to try something new. It's something that we really kind of do and have a sleepless night before a new implant or something, so it's really very much part of our culture.

If you look at the number of trials that people have tried, you know, interventional trials in stroke medicine or SynCardia device or Jarvik, there's lots of different ones that are examples of where we're struggling with enrollment, and I think the point was made that maybe we should involve families more in that piece because I think that they may end up being, with some distance in time, advocates for getting this information. But it is a real

challenge that's out there, and I think it's one that the clinical community needs to work on maybe even more so than the Food and Drug Administration as it's working on other things.

DR. SILVERSTEIN: Martin talked about feeling the pain, and I think we really do feel that pain because if I'm a reviewer and I'm involved in a study and we approve a study and the study is not going well, we really do, I hope we do, we look at it as our failure. We look at it, and so not infrequently. So we get annual reports, which includes how many patients got entered into the study, but also if we communicate with the sponsor and we find out they're having trouble with the study, the first thing I'll do, as a reviewer, and a lot of people do that here, I'll go back to the clinical trial design, and I'll look at the inclusion/exclusion criteria, and literally, I'll call them again on the phone and just say, hey, let's talk about this.

On the other end of it, it's not easy to be proactive all the time, and you can be receptive to requests for modification. And I do think that we're very open to that, and I think most people out here are probably saying you're kidding me, but I'm not. We are very open to that; we just rarely get those calls. I mean, I picked up the phone a couple of times or I sent an email, and I have said, you know, it looks like you're having trouble with enrollment, let's talk, and they have then called and said, yeah, we're having trouble, and they're pretty open to that.

So I think it's got to be a back-and-forth discussion, and I think Martin and anybody here at the FDA would probably tell you that culture has changed here a lot. Not everybody, not to the full extent, but if a trial, I just had a discussion with a sponsor about a week ago, a couple of weeks ago, and I knew they were having trouble with enrollment, and we changed a few of the inclusion/exclusion criteria. I don't know if it will help; we're hoping. So be open, be willing to reach out and to say, hey, we're having trouble. Don't keep it hidden in the shadows; let us know about it.

One last question.

MR. KROSLOWITZ: Yeah, Bob Kroslowitz. I had a question for Leonardo.

Leonardo, you mentioned just a few minutes ago that you are able to use data that's submitted through other clinical trials to do modeling or design, you know, different designs. How are you able to do that, I mean, are there consent issues around that, or how does that work?

DR. ANGELONE: Let me rephrase. These are data; they were submitted and approved, so (510)k cleared and PMA devices. They were not clinical trial data; they were bench testing data.

MR. KROSLOWITZ: Oh, okay.

DR. ANGELONE: I can't talk from Office of Counsel, but of course, we had approval from Office of Counsel. I would not exclude that this is also possible for clinical trial once the PMA or the (510)k has been approved, okay, because it's part of the evidence. And, of course, there was a lot of work in anonymizing those data and then made them available. We didn't use them internally; we just show what is the kind of the data from different groups.

MR. KROSLOWITZ: So I'd imagine, though, with clinical data, right, that that could end up being an issue, right, because you're only allowed to use the data for what you have consent to use it for.

DR. ANGELONE: I want to say there is a study published in *JAMA* a few years ago that used PMA data submitted, again, that showed the effect of CRT devices on male and female population, and I believe this was data that were PMA approved by the FDA. But, again, this is something that maybe offline I can provide that reference.

MR. KROSLOWITZ: Thanks.

DR. ANGELONE: Sure.

DR. SILVERSTEIN: Okay, I've cut off 5 minutes of the break again, but we're going to take a break now for about 10 to 12 minutes, and we'll come back, and we'll talk about research networks and infrastructure, so thanks again to the speakers for some great talks.

(Applause.)

(Off the record at 3:04 p.m.)

(On the record at 3:18 p.m.)

DR. SILVERSTEIN: And I'll read the question out loud, but you can see it yourselves. The question is can data from an adult population be extrapolated to pediatrics? Yes, no, and sometimes, don't know, I'm hungry, whatever you want to say.

(Audience poll.)

DR. SILVERSTEIN: So, as we go through our poll question again, can data from an adult population be extrapolated to pediatrics? Yes, no, sometimes, don't know. And I think actually this is one that I think where all three of them apply, yes, no, and sometimes, and I think that kind of covers the gamut. Most people said sometimes, and I think that's actually correct. The information we heard today from Jackie Francis kind of points to that, but I would say also it depends. What Randy said is the words you don't want to hear from the FDA but I think actually a lot of times opens the door.

So we're going to start out with the next session, and this is on Research Networks and Infrastructure, and we're going to start off with Barbara Christensen, who is the Senior Director of the National Cardiovascular Data Registry and Accreditation Services at the ACC, and she's going to talk about the Potential of Mature Pediatric Specific Registries.

MS. CHRISTENSEN: Good afternoon, everyone. Happy to be here. And as said here, what is the potential of a mature pediatric specific registry? So, when I was asked to give this presentation, I thought the best way to do that is to give you an overview of the ACC's IMPACT Registry. As you know, we all love our acronyms. IMPACT stands for Improving

Pediatric and Adult Congenital Therapies.

At the NCDR, which is a division within the American College of Cardiology, our mission is to improve the quality of cardiovascular patient care. We want to provide information, knowledge, tools, implement quality initiatives, and support research that improves the patient care and outcomes. Over 20 years ago a group of very visionary cardiologists wanted to measure what was happening in the cardiac cath lab, and that was the birth of the NCDR. We are the largest, most comprehensive outcomes-based patient registry repository in the United States, and we have a total of 10 registries.

With our beginnings in 1998 up through 2016, you can sort of see the timeline where we have added different programs: over 2500 hospitals, close to 6,000 providers, and greater than 40 million clinical records across these 10 programs. What we're really here to talk about today is the IMPACT Registry and the pediatric community.

IMPACT, as I said, is looking at procedures for pediatric and adult congenital heart disease. You can see the procedures that are captured in this registry by measuring the prevalence, demographics, management, and outcome for these catheter-based procedures. We recently added, with our last update, EP and EP ablation procedures and pulmonary valve replacement. It now includes an optional follow-up module.

So let me just talk a little bit about the type of data that's captured in the registry. This is just a visual representation of the form that people can download to get an idea of what data fields are collected. Hospitals enroll in the registry program. We have a contract with hospitals that allow for the submission of their patient data to the warehouses within the ACC. And these patients who are entered, it's all eligible patients who meet the inclusion criteria are expected to be entered into the registry. It's not a sample; it is all patients who are having these procedures that meet the inclusion criteria.

As I said, we launched in 2010. Currently, we have 109 U.S. hospitals, mostly

university medical centers, children's hospitals. We have two international. And since I made this slide 2 weeks ago, we've added two more in Canada, one in British Columbia and one in Alberta, and we have one in Queensland, Australia. We have over 95,000 patient records.

So, data is used for many purposes within the NCDR and people ask, well, how do you capture the data? In three different ways, to us. Through electronic health records, which is mostly with our outpatient registry programs. The data is extracted on the back end out of the HER, causing no disruption to the workflow in the ambulatory care center setting. The vast majority of our hospitals provide data through either the third-party certified software, which can interface with your hemodynamic systems, your laboratory systems, your ADT systems or a web-based data entry, which is all manual data submission. But we provide that option for those smaller hospitals who may not have the resources to purchase a third-party software solution.

So, data is captured, and it comes in to the NCDR, and it's used for multiple purposes. There's different stakeholders. Data is used primarily for quality and performance improvement, but what we're really here today to talk about is how can data out of registries serve a purpose for research and surveillance?

The number one question is how good is the data; can I trust that data? The NCDR has invested a lot of time and resources into providing quality data. There's a series of data checks when the data is entered; it also is then validated against those checks for errors and completeness. Some registries have an adjudication process; all registries have a national audit program which evaluates for accuracy and reliability, and it is completed by an independent organization. We also provide data outlier reports, meaning if all of your patients are a Class III angina, that's where you have no complications, you're an outlier, you're going to get a notice to say it's not that we don't believe you, but we want you to

double-check.

Over the years we've been working with the FDA on numerous projects. Probably one of our most successful has been with our transcatheter aortic valve with a partnership with the Society of Thoracic Surgeons. Data from that registry has been used for postmarket surveillance and continuing access protocol studies, and the NCDR does see an evolving role with the FDA as we move from clinical trials into clinical practice, the use of registries to meet these objectives.

Our goal is to provide high quality, real-world data to support the device manufacturers' research needs through these various things and ultimately to increase efficiency across the healthcare spectrum.

One of the biggest questions we also get is what's the relationship with industry? I'm not going to go over each of these points, but these are sort of the big bucket questions. What's my access to data? How can I use that data for research? Can I do drug or device comparison? Who owns the data? How can it be used? I will tell you that our relationship with industry has been very positive over the last few years, there is a statement of work that is required, and data is provided back to industry for their own analysis and to meet their reporting requirements for the FDA.

ACC owns the data. Actually, hospitals own their own data; the ACC owns the de-identified aggregate dataset. However, there are times where industry, if you're doing a continuing access study, you may, that may be ownership of, industry may own that data. It just depends on the nature of the contract and the relationship.

Currently, we don't allow for direct device-to-device comparisons; however, if you're going to compare your device against a group of devices, that might be allowed. We just have to see the protocol.

So, in summary, what I want to say, when we're looking at evaluating registries for

use, is it pediatric specific? We can say yes for our IMPACT Registry.

Is it mature? Yes, it's been around for 8 years, and we have close to 100,000 patient records.

And is there a potential? Well, the potential is, clearly shows that it can be used for postmarket studies, can be used for device-specific studies, and multiple procedures can be captured.

I have to say that there are some limitations right now with the IMPACT Registry. It is only looking at those seven or eight procedures, so it's not going to capture everything that you need. Sorry.

So I will stop there. My time is up, but if you have additional questions, you can check us out at cvquality.acc.org, or I'm happy to talk with anyone, and my contact information is in the app. Thank you.

(Applause.)

DR. SILVERSTEIN: Thank you.

Our next talker is going to be Peter Margolis, who is the Learning Networks Program and PEDSnet co-director of the James M. Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital and Medical Center. And Mr. Margolis is going to talk about, Dr. Margolis, I'm sorry, disease-specific learning networks to generate clinical data.

DR. MARGOLIS: Thanks. It's a pleasure to get to talk a little bit this afternoon. The bottom line in this presentation is that by linking clinical care, continuous improvement in research, we're able to accelerate the process of evidence generation and put it into practice. The continuous cycle of learning application and feedback is what's becoming known of the learning healthcare system and the idea is that it should drive the process of discovery as a natural outgrowth of patient care to ensure innovation, quality, and safety and value in healthcare, all pretty much in real time.

The central hypothesis of the learning healthcare system is that by designing and implementing a healthcare system that eliminates the boundaries between clinical care improvement and research and by engaging everybody as part of one system, we'll be able to produce better outcomes, better experience for families, faster research, and lower costs.

The National Academy of Sciences has identified five main requirements for a learning healthcare system. The first is to link personal and population data to researchers and practitioners; the second is to provide real-time guidance for better care in treating and preventing illness; the third is to enhance the knowledge base on the effectiveness of interventions; the fourth is that actions need to be taken by every stakeholder; and the fifth is that there's a recognition that making these kinds of changes is hard, and we have to be able to change complex systems.

So our focus has been on creating large networks of patients, clinicians, researchers, and clinical care units that work together to do all of these things, what we call learning health system networks or learning networks for short, and our goal is to run the cycle faster. Reducing the time from discovery to application means faster impact on health.

So this work grew out of some efforts with the American Board of Pediatrics and the American Academy of Pediatrics, beginning in about 2003, to create systems that would overcome a core challenge in pediatrics that we've been talking about all day, which is that serious illness in children is rare, and the only way to make progress is through an ability to collaborate to collect and share data and translate new knowledge into practice so that outcomes improve.

So this slide shows the results of what's taking place in four of the most mature networks that we support at the Anderson Center. In the upper left is a network called ImproveCareNow. It's a group of pediatric gastroenterologists who are working together on

Crohn's disease and ulcerative colitis. What you can see is the increase in the percentage of kids in remission since 2007. In the upper left.

In the upper right are data from the National Pediatric Cardiology Quality Improvement Collaborative. This is a network focused on kids with hypoplastic left heart disease. It shows a 50% reduction in mortality for kids in the first year of life during the inner-stage period in which children are undergoing multiple heart surgeries.

The lower left is data from the Solutions for Patient Safety Network; that's a network of 130 hospitals across the country. This shows a reduction in urinary tract infections. I'm not allowed to publicly show the data on serious safety events. There has been a 50% reduction in serious safety events across 130 hospitals.

In the lower right is the data from the Ohio Perinatal Quality Collaborative; it's 52 out of the 54 birth hospitals in the state of Ohio showing a 75% reduction in elective preterm delivery.

The Anderson Center serves as a coordinating center for these networks, and today we support 600 clinical sites and 275 hospitals in the U.S., Europe, and the Middle East. And what I'd like to do is to illustrate how we've met the requirements of a learning healthcare system.

So the first requirement is to link personal and population data to researchers and practitioners. We have focused on ways to make the data go where it needs to, and with funding from the Agency for Healthcare Quality and Research, my colleague Keith Marsolo and John Hutton created a registry architecture in which data are entered once during the course of care and then used for clinical care improvement and research.

So once the data are flowing, you can satisfy the second requirement of the learning healthcare system by providing real-time guidance through tools like pre-visit planning and population management.

So built on this architecture, this screenshot is from the ImproveCareNow registry, and it shows the automated reporting tools that are available for chronic care management. In the upper right are tools that are related to research and analysis, the ability to identify patients through queries.

As part of our work through PCORnet, we've been able to build large systems of interoperable data that link EHR from about 100 institutions. One of the networks in PCORnet is PEDSnet, which is currently comprised of eight of the largest children's hospitals in the country, and this has created the capacity to access data about diagnoses, labs, medications, visits from more than six million children.

We've also shown that we can enhance the knowledge base on the effectiveness in interventions. Here is a slide showing a comparative effectiveness study comparing the use of anti-TNF-alpha agents for the treatment of moderate to severe Crohn's disease. A trial had been on adults; it was not possible to do a randomized trial in pediatrics because it was felt to be unethical, so we were able to use the data from the registry to replicate the findings from a large trial demonstrating the effectiveness of the medication.

In a learning healthcare system, a key and difficult requirement is that actions need to be taken by every stakeholder; in fact, if you look at the gap between current outcomes and what we want to see, the problem isn't that people don't care or they don't have good ideas. Everyone cares. We just don't have a good system for translating this evidence into practice. So with funding from the NIH's Transformative Research Award, we were able to address the question of whether or not we could create a system for chronic illness care by harnessing the motivation and intelligence and capacity of people to work together to combine their lived and professional expertise to solve problems to improve health.

When patients get together, they start to solve problems. Jenny David was chair of the ImproveCareNow Patient Advisory Board, and she published this article in the *New*

England Journal last summer about her lived experience as a patient and a researcher, about the skills that she had cultivated as a researcher to address a problem that she saw and felt as a patient.

Zach Wallace, a 9-year-old, created a video of how he inserts an NG tube every night to give himself enteral feedings, and this unleashed, in the network, a kind of ALS-like challenge in which care teams also wanted to learn about what this was like because most doctors have actually never put down an NG tube. This is a slide of the Nationwide Children's GI team proudly displaying the NG tubes that they put down. And patients got together to address problems that they had, like creating an ostomy tool kit that young people who, most doctors have never lived with an ostomy, so they wouldn't think about what you would say if you needed to go to the swimming pool in a bikini with your ostomy.

So to combine the power of all these contributions from patients and their clinicians, we developed the exchange. It's a little bit like Pinterest; it allows you to pin your ideas and share them with the community for remix and reuse, and one of the innovations that emerged from the community, from a patient, a clinician, and a statistician, was the idea of actually creating a platform that would allow NM1 studies to take place.

This is a slide, this idea has matured into a study that's being supported by a collaboration with UCSF in which patients and clinicians are collaborating to design and run their own NM1 studies. One of these is a PCORI-funded trial called PRODUCE that is focused on a specific diet that patients with Crohn's disease are interested in to evaluate whether or not it can improve outcomes at an individual and population level.

The result of this learning health system is that it's become a platform for research, and ImproveCareNow is one of the networks that's possible to utilize the network for a wide range of topics, from generating real-world evidence to optimizing care to engaging patients and physicians to conducting efficacy studies to postmarketing surveillance to

testing new innovations.

The learning health system model overcomes some of the artificial barriers between clinical care improvement and research. It's addressing the fifth requirement of the learning healthcare system, which is that there is no simple path forward and that we have to work together to change large systems.

As I said, currently there are 12 networks in operation, the system, and the platform has become a way to learn and apply across many diverse settings and across a diversity of contributors, patients, clinicians, and researchers, who are all working together to support learning and the reliable application of knowledge to improve health.

Thanks.

(Applause.)

DR. SILVERSTEIN: Our last speakers, we're going to perform a duet. We're going to have Daniel Benjamin and Ed Connor. Daniel Benjamin is a Kiser-Arena Distinguished Professor of Pediatrics at Duke Clinical Research Institute, and Ed Connor is the Chairman and Chief Scientific Adviser for the Institute for Advanced Clinical Trials for Children. They'll be discussing Pediatric Clinical Trial and Product Development Infrastructure.

DR. BENJAMIN: I thought you were going to ask me to dance with Ed. Ed looked at me like he was very uncomfortable, and I think the same thought went through his mind.

(Laughter.)

DR. BENJAMIN: Danny Benjamin, and I'm Professor of Pediatrics at Duke University, and I'm going to be speaking to you just from experience. At Duke Clinical Research Institute, each of our 14 faculty spends between 2 and 5 years in a joint full-time employment at FDA to get some regulatory expertise. We have about 50 or 60 operational staff working on our trials across 9 different therapeutic areas in pediatrics. This is all regulatory compliant data and molecules and devices at over 200 sites, and we are

averaging about 60 publications per year, which our site investigators like because it gets them on the masthead for promotion and tenure. Thirty-five regulatory compliant clinical trials completed thus far. About half of those are industry sponsored. That's our publication right there, which our enrolling partners tend to like given that enrollment is really the key to trials and the dissemination of the data.

When I think about trials, whether it's for a molecule or for a device, kind of what can go wrong and really, you know, do I have the right product and the right patient population and the right exposure, whether that's a molecule or whether that's what the device itself does. Is the design right and are the endpoints right, and do we have the right recruiting strategy? And other than that, enrollment is actually pretty easy except for consent.

When we think about our planning and operations and our real-world evidence, we think about going from, one might be roadblocks to regulatory success, we really see one of the big hurdles is folks who are clinically extremely expert and extremely passionate around children's health, typically at the site level, who often will be talking past folks who really know a whole lot about drug development, whether that's at the FDA level or at the company level, and connecting those two groups of folks is a big part of what we do, whether it's through the pediatric study plan or the investigational plan and the design. You know, it's just not good enough to think the design should be X because I think it should be X, right, because I'm an expert in this area. It's got to be based on data for every line that's in the protocol. I won't walk you through all of this, but the list goes on and on as it relates to the design of successful trials.

Now, in our own experience, we have done 10 FDA label change negotiations and had over 20 pediatric product submissions to FDA for regulatory compliant data, and in addition to that, we do not only the pediatric study plans and the investigational plans but

also design optimization.

And a lot of this expertise was initially really built up through the Pediatric Trials Network, and that network is funded by the National Institute of Child Health and Human Development. We've really benefited from partnership with the American Academy of Pediatrics in order to have the successful groundwork laid for that and an ongoing active participation across the divisions at the Food and Drug Administration. That was originally awarded in 2010 and renewed in 2018.

And in that network there's 70 drugs studied, 22 active INDs, this is on the drug side of it, over 7,000 patients, total about 1,000 patients per year. If 1,000 children enrolled in regulatory compliant data doesn't sound like a large number to you, you probably haven't enrolled in that many pediatric trials. We've been very, very fortunate with our enrolling partners and with our partners in regulatory and elsewhere. Within the PEDs Trials Network, we started to expand to not only the enrolling sites, but also other networks that are actively enrolling and partnering with us with data. And then with our most recent device trials, it's not as extensive as our drug trials, these are the ones that are completed, and these are the ones that are actively enrolling.

Just for the organizers, are Ed and I splitting the 10 minutes or, oh, I get 10. Oh, my gosh. I should've said all that much slower.

(Laughter.)

DR. BENJAMIN: I feel like I've been up here, I thought I only had 5 minutes. I'm like, man, I got to get through this.

DR. SILVERSTEIN: Are you telling us that the five calls that we had didn't clarify any of this?

(Laughter.)

DR. BENJAMIN: No, no, no, no. I'm telling you that my ADHD kicked in right at the

last minute, and as soon I was introduced, I was like, oh, my gosh, what am I going to do up here?

All right, so let me pass on, the nice thing is since most of you are actually checking your iPhone while I was going through slides anyway, and I've been watching you do that all day, from the back, I'll just give you a couple of points of experience about enrolling in trials, whether it's devices or in molecules, and it's only based on doing it thousands of times.

Number one is the development of your sites. One of the things that I'm really happy with what we do for that is that in each new trial we've been able to convince our sponsors to take on two things. First of all, whatever estimate of sites that you think you need, you should triple it. And then if the person who's pitching the trial to you has never actually done a Part 11 compliant trial before, you should triple it again. And then whatever that number is, then we add 10%. And that last 10%, we can try to convince the sponsors of that right away. Those are the sites that are new and that have never done or have rarely done a trial before in this particular domain. Those are your at-risk sites.

Now, the sponsors get a little bit nervous about that, but those are some of our highest enrolling sites sometimes. They'll really surprise us. And one of the nice things about it is one of their up sides is they don't have competing studies, which is awesome for you as a sponsor, because one of the paradoxes is once a site gets to be successful, everybody hears about it, and then everybody who's doing the next pulmonary hypertension trial or whatever the case may be is all rushing for those sites, and every potential project that comes through, we're really seeing this quite a bit in neonatology. The second thing that we found to be very successful with the sites is we've committed to them up front on a publication plan.

Now, for an industry, you know, this is really not your priority, right? And I get that,

just like finding venture capital, I mean, my eyes glaze over when I hear about you guys having to find venture capital; I mean, it sounds like vultures, and it just is a bummer for you, but on our end, if we don't have that plan going up front for those site investigators, they are really not going to be super motivated to get a big lift going. And just wave, wave at me, okay? Don't be shy about waving at me about my time being up. Having that plan with them really links them in partnership with you and essentially prioritizes your study.

Two or three things that we're actually trying in the next 24 to 36 months: The newest one that's coming up now is kind of e-consent. And one of the things that really plagues children's studies is the study coordinators spend so much time racing around the hospital looking for children and, of course, the parents have the child who's in the hospital, very good, but they've got three or four at home that they've also got to take care of, so they can't consent at the bedside, let alone if you need the fatal flaw of two consents. So we're now piloting e-consents, and we have large hope for that.

In addition, the other two final things that we're trying to pilot, more and more use of bringing in the direct EHR data into the trials, which fields we can trust from which hospitals and which we can't, and finally, direct-to-patient enrollment for peds studies and trials is something we're looking at not this calendar year but the next.

Thanks for that, and I'll leave it over to Ed.

(Applause.)

DR. CONNOR: Thanks, Danny. What I'm going to do in the next few minutes is to talk to you about an initiative that we've been involved with for the past few years, and it's called the Institute for Advanced Clinical Trials for Children and some of the challenges and progress and status of that organization.

So the Institute for Advanced Clinical Trials for Children actually arose out of a meeting at the Academy of Pediatrics in late 2014 in which a group of clinical trials

stakeholders got together, not so much to lament the challenges of what we need to do in pediatric clinical trials, because we've had lots of meetings around that, but rather to begin to think about what are the new solutions, think about a new way of putting together some of the fragmented parts of the clinical trials ecosystem, and then creating an opportunity to create a catalyst, ideally an independent organization that can begin to carry out that mission.

That challenge was taken up by the Critical Path Institute, which comes out of the Critical Path Initiative and has been around for 10 years, and putting together these kind of public-private partnerships and consortia of multiple stakeholders that created the Pediatric Trials Consortium, which represented 30 different representative stakeholders from industry, academics, parents, etc., to come together to basically create a roadmap for the kinds of things that we needed to do to begin to think about this as a different way and, as Danny pointed out, to focus on activities that were related to product development and the delivery of products to kids. That group took a few months to put together a roadmap, and then it took that roadmap and used it to launch a separate 501(c)(3) that became the Institute for Advanced Clinical Trials for Kids, and that institute was formally launched in March of 2017 and now has its legs in terms of getting engaged in this process.

The organization was established to include the timeliness and quality and the impact of clinical trials for innovative medicines and devices for children. It is specifically focused exclusively on innovative product development, which is really on patent product development, generally, and products that are destined for labeling. It has, as has PTN and DCRI, a multicenter coverage, so it's agnostic as to what kind of materials we're developing. We just care about those things that are going to have an impact in kids and that we can help advance with some efficiency and other characteristics. We talk a lot about cross-stakeholder engagement, particularly patients and parents and others in the process, and

that's a founding principle of this organization, and obviously, to do anything in clinical trials in kids, it needs to have a global reach.

This 501(c)(3) is a public-private collaboration, and it specifically, as I mentioned, and exclusively, actually, designed to pay attention to those things that are related to things that are driven to ultimately labeling, and so it brings all of those stakeholders, including industry, into the process. It is focused on the principles of pediatric product development, which is very different than understanding the disease or doing other things that we have in academic pursuits; it's specifically driven by the skills and an understanding of how to do that process. And it's really focused on sustainability. One of the problems in the system is that we keep building infrastructure and then it sort of gets teared down. Some of the things that Danny talked about are some of the more sustainable of those activities, but even for individual projects, we build infrastructure, and then it sort of goes fallow, and we have to learn it all again, over and over again.

Efficiency, which is there's a lot of inefficiency in the system. We know right now that even though many drugs are not approved for kids, and while we're doing a good job at correcting some of that, it still takes about 9 years to go from an adult label to a pediatric label, and it's about that same time frame for pediatric approvals in devices, also. But even if we become 1,000 percent efficient, 100 percent efficient, we still have challenges in pediatrics, and that's where innovation in trial design and in thinking about the development strategy, not to change the bar for children but to change the way in which we can efficiently get there, is really the mission of the organization.

We work in four main areas. One of them is in strategy and planning. That specifically is under the mantra of us all trying to get it right the first time. A lot of trials that we put out into the field in this space of product development fail or stall and don't end up with actually delivering what we need.

And we work both in the pre-competitive space with sponsors and stakeholder groups to address some of the key challenges in clinical trials development, whether that be application of tools like extrapolation, etc., or other approaches to feasibility assessments, which we actually do only modestly well as an ecosystem. And we serve as an independent advisor and consultant to sponsors for proprietary projects, and that includes, at one end, looking at various tangible projects like projects, protocols, pediatric plans, etc., but also in working with some of our large sponsor members to be able to really understand where the pipelines are going and how we can begin to work together to really begin to plan for product development as well as react.

It also involves an infrastructure of clinical sites that are product development centers of excellence that are being built now, which includes a whole variety of various elements, not the least of which is the work that Peter has talked about in linking to quality improvement metrics so that this is really a sustainable and healthy network of product development specialists as we go forward.

We also work in the block and tackle parts of the processes for making that happen, and best practices. And obviously, in leadership and advocacy, including and maintaining a sense of urgency, part of the problem is that we all need to do this well because kids are sort of waiting at the back end for the delivery of these products.

The organization is structured as a membership organization, so it's supported by membership grants and donations. It also, along with DCRI, has a grant from the FDA to begin to support the development of this kind of infrastructure and then ultimately has a business plan that was associated with the Pediatric Trials Consortium to create sustainability over time, through revenue that's generated through the work that the institute does.

Senior leadership in the organization and all of its components, which has developed

quite nicely over the last year or so, has all been driven by folks who have experience in both academic product development and in industry. Many of us have actually physically been in both of those chairs and so have a sense of what the challenges are on both sides of the coin, and that involves management of IAC, many of whom are here, including a new CEO we've recruited recently, and all are dedicated to the specific mission of delivering on the promise that the organization was created for.

And then a network of partners and other folks, collaborators. We don't see this organization as being hierarchical in any way. It really functions as a catalyst and to collaborate with others to be able to deliver on the promise that we've been discussing.

What we try to do is to bring all of the elements of product development to the table, and that includes many of the things that you can see around here and then engage the ecosystem of many experts across the country to deliver on that promise. So that includes a number of the people that are listed here, including folks like the PEDSnet organization and PCORnet and then the device connections through the National Capital Consortium and with the FDA consortia and then the other components of product development that you can see here.

The network has evolved. As to the team, it has about 29 centers. The goal was to start with about a cohort of somewhere between 30 and 40 centers through 2018. It is also based on the development of the inclusion of eight of those centers, which are the PEDSnet hospitals, which have deep access, CEHR, and allow us to generate that data to be used in feasibility, both protocol feasibility as well as recruitment of other aspects of feasibility.

The site network has a clinical and operational lead at each of the centers, and there will be sort of common training and common processes and metrics. And there's a lot of peer-to-peer engagement. A lot of the challenge here is really working individually with centers and pediatric folks to deliver on this work. And in addition to that, there is

involvement based on patient engagement tools and other methods to support the staff at each of the sites.

The goal is to create about 100 sites for the representation of being able to match what we think is the pipeline of work that's coming through over the next several years, and we have strong relationships with C4C, with Canada, with Japan, in addition to the U.S.-based programs, and a number of specialty networks.

I just want to mention very quickly that there are two other primary organizations in the rest of the world that's being developed with this public-private partnership in mind. One is C4C in Europe, that Danny has mentioned, and certainly that organization allows reach through their organization to a tremendous resource elsewhere. And in Japan a similar organization is being created. And the goal here is not to create these systems that are identical, but rather to create global interoperability in the long run, and that's ultimately what we'd like to try to establish.

I'm not going to go through examples too much in the interest of time, except for the really important ability, through the connection with organizations like PEDSnet, to access data through the EHR and other systems that allow us to really fine-tune our ability to create trials that are feasible to start with, and to use that kind of data, including in this case, you know, many millions of data points for kids in Type 2 diabetes, to really assess how we can get through both the development of trials and sensitivity for inclusion and exclusion criteria as well as other programs.

There's a lot of work in the non-proprietary space, which include a whole variety of different kinds of things. We're working, for example, in a program with the Parent Project Muscular Dystrophy and Critical Path, who are evolving tools for disease progression and Duchenne, to work on platform trials that are now coming together. And there's a number of other programs that are in the precompetitive space.

The competitive space or the proprietary space is also an arena where we're now moving projects through the process, both in terms of advice and guidance as well as actual implementation at sites.

So I think, at the end of the day, we've been able to demonstrate over the years, I mean, we've been doing this for many decades now. But we know that we can do ad hoc product development; we've done that when we had no other way to do it. We also know that when it's really important, in the early days of HIV and other times when it was really, really important to move things through the system, we can do that when all of those things are aligned.

What we'd ultimately like, on the other hand, is to have a system that is totally, that is a global system for being able to do product development. Where we are right now is in work that is integrated and interoperable, and you've seen from the discussions that we've had so far that there are a number of opportunities to be able to do that. So I think all of us are excited about the potential for using these kind of resources to really have an impact on the quality and the importance of trials that we bring forward for kids.

It takes a large village to do that. This is only a small representation of the people that are involved, and it includes commitments on the part of a number of companies that have been part of the trials consortium as well as in several instances moving forward with IAC, Critical Path Institute, the National Capital Consortium, and the FDA consortia, PEDSnet, and PCORnet and the other folks that are listed here.

So thanks very much.

(Applause.)

DR. SILVERSTEIN: Sometimes the price of success results in needing extra time, and so we apologize. We wanted to have a lot of good speakers here, and we've had some great speakers, and unfortunately it just limits the time, so we apologize about that.

So we're going to conduct a brief question and answer session. Just to let you know, the public comment period, which will involve three brief discussions, will be following the question and answer, and then we're going to have a directed expert panel discussion.

So Mark.

MR. DEL MONTE: Good afternoon. Thank you to an excellent panel; that was superb and informative. I'm thinking of a comment that Dr. Newman made first thing this morning and then following up on something that Dr. Connor and Dr. Benjamin both said, but just I'm thinking triple it and add 10%. In that precompetitive space, before you actually have a product, before you're worried about proprietary information or confidentiality, is there more that we could be doing to invest in that precompetitive period so that sponsors can start on second base, on third base, instead of at the beginning, so that we don't reinvent wheels and gain inefficiencies and all of that? And I wonder if there's an opportunity for us to think together about what kind of policy innovation would be helpful to build out that precompetitive space.

DR. BENJAMIN: So if I had to think about a couple of areas that have real potential, is in the area around, and I hate to use the term registry, but in the area around product-agnostic diseases where we cannot extrapolate and we're not sure why we can or can't extrapolate. And that's for both drugs and for devices. Because the lift, when you move from I can extrapolate to partial extrapolate is big, and then the lift from partial extrapolation to no extrapolation is enormous.

And so it's around that area of study design, what should the endpoints be, how far can we extrapolate, how much can we extrapolate, that I think that policy and innovation really has a chance to interact in a way that's good for not only child health and for companies and for stakeholders, right, because even if we're not able to get that particular device off the ground, it will be better for the next device, and it will certainly be better for

child health because we'll be able to treat it at the bedside.

DR. CONNOR: Yeah, I think that there's a lot of opportunity for pediatrics to be able to be in that space, to really be able to utilize the global resource of pediatric patients, to be able to focus on areas that are actually really going to be deliverable. So the stuff that Danny was talking about is important also to take to the next step, which is to actually find examples of where we can demonstrate that that is an advantage. And I think in some of the areas where there's a lot of challenge right now, I mean in device development, in drug development, in Type 2 diabetes, and in places like muscular dystrophy, there are a lot of drugs in development and a lot of challenges in how those drugs are going to get moved through the pipeline. So finding ways in which we can use the patient population, understand how we can best use extrapolation and other tools and apply them in the real-world setting is really important.

MR. KROSLOWITZ: Bob Kroslowitz. I have a question for Barbara.

Barbara, specifically related to registries in the cardiovascular space, it seems that these days registries are like opinions, right; everybody has one, and in the cardiovascular space specifically, we were counting earlier, there's about 20, right, for congenital heart disease and cardiac surgery. So when we're talking about, you know, generating real-world evidence from registries, how do you decide where to go?

And with the limited resources within in the institutions, in pediatric institutions, you have to wonder with that many registries, really, where and if there is quality data, right? Out of 20 registries, I can't imagine that there is somebody in a hospital entering all the same data into all 20 registries. So somebody is not getting everything, it would seem, so I have a hard time understanding how really, with so many registries, we can really say that there's quality data that we can obtain from these registries. And how do you decide which one to go to?

MS. CHRISTENSEN: Well, it's a great question, and I think most anybody who's in the C-suite is asking themselves that same question, where are we spending our resources? Obviously, from the ACC's perspective, one of the things is, is it a national registry? What's the breadth of the registry? What problem are you trying to solve at your hospital, and what registry might be able to provide a solution for you? You know, from the cardiovascular space, obviously, the STS is the largest, most comprehensive cardiac surgery database. For interventional cardiology procedures, I would say the IMPACT Registry is the most comprehensive, given that you have 109 U.S. sites across the country representing all geographic locations, cities, rural, a spectrum of that.

So I think some of this is you have to ask yourself the question of what's most important to you. You know, I'm not aware that there's 20 cardiovascular pediatric registries. I know there's a few homegrown and there's some smaller networks, but I would look at what's the breadth, what do you get out of that registry, what kind of benchmark reporting are you getting, what is the comprehensive nature of the reports that you're getting out. And, again, it's what's most important to your facility and what problems do you need help with.

I don't know if that answered your question, and you know, cost is always a consideration, and it's usually not the cost of the registry themselves; that's not where the cost is. It's the human factor of someone who's abstracting that data and interpreting that data and entering that data. That's where the cost comes in.

MR. KROSLOWITZ: Yeah, it seems like, and a lot of the discussion today is we're struggling, right, to get data for a small population of patients. And so such a small population of patients with data spread out all over the place, it seems like we could be, you know, somehow doing a better job at that. Thanks.

DR. SILVERSTEIN: Okay, we're going to move ahead to the public comment period,

and our first speaker is going to be Roberta Bursi. And you can come forward, please. Maybe you could introduce yourself, and thank you.

DR. BURSI: Thank you very much. Good afternoon, everyone. I would like to start to thank the organizers for the excellent meeting and for the opportunity to tell you about InSilico Trials Technologies. InSilico Trials has a division to democratize modeling and simulation in healthcare and increase pace of innovation by leveraging a synergy of scientific, technological, and regulatory know-how, and our mission is to drive technology trials and access from the scientific community to medical devices and pharma companies through insilicotrials.com, which is a secure cloud-based computational hub. We are board members of Avicenna Alliance, and we are collaborating with the FDA on InSilicoMRI, as previously discussed earlier this afternoon by Dr. Angelone. And we are collaborating with the EMA on cybersecurity.

The challenges of pediatric devices landscape are not specific to the devices, medical devices. In pediatrics we have to deal with highly specific valuable patient profiles, very specific and orphan diseases, high-cost clinical trials, lack of presence of published data to use off-label drugs, as well as the fact that the medical devices market is a niche market with respect to the global market as well as in pharma, these are all difficult challenges with pharma work as well. So it could be very valuable if the two worlds would speak with each other and share the experiences, and InSilico Trials is a great supporter of the close work and synergism between the two worlds, particularly in relation with the development of device-drug combination products.

I would like to take an example from the pharma very quickly, the addendum to the guidance of the ICH E11, which has shown up in April this year, which explicitly says that modeling and simulation is a tool to address knowledge gaps. In the pediatric development ecosystem, example by knowledge gaps, and in this addendum explicitly, modeling and

simulation is mentioned, recommended for quite a list of activities among extrapolation, managing risks. Those nonclinical trials simulate clinical trials.

I would like, then, to conclude by saying that the medical devices pediatric development landscape is really characterized by individual peaks of excellence and vast areas of unmet medical needs. And insilicotrials.com presents an opportunity to bridge these peaks and these gaps across the pediatric landscape in order to accelerate the innovative and cost-effective products for this highly vulnerable patient population.

With this, I would like to thank you for your attention.

(Applause.)

DR. SILVERSTEIN: Thank you very much for hitting on some of the themes we've heard about today. Juan Espinoza is going to follow up with a discussion of clinical informatics.

DR. ESPINOZA: Oh, the PowerPoint doesn't look great. Good afternoon, everyone. My name is Juan Espinoza. I am the co-director of CTIP, which is the PDC that's based at Children's Hospital Los Angeles. I'm also our institution's director for clinical research informatics. I want to thank the FDA for this excellent event and for allowing us the opportunity to address the group today.

One thing that we have been thinking a lot about at our institution is how do we leverage our clinical informatics programs to support the development of safety and device-monitoring systems. We feel that, as academic institutions, as pediatric centers, we feel we have a duty and we have a responsibility to enable safety-related research for our patients, and as long as we are developing these informatics infrastructures, we should be able to use those to support the development of safety monitoring systems. I won't go over the why, because we're all here, so you all know. There are several things that will be necessary to effectively implement such a system. Many of the speakers today have

addressed these. I just want to highlight that Dr. Martin Ho and I are on the same page about needing device-specific PROs to really capture that patient experience.

And two things that we'll have to think about long term: One is what are the regulatory considerations around how does data flow through a national safety and surveillance system? Does the current regulation, does HIPAA allow for that, and if not, will we need separate processes for that because it is probably impractical to consider every single patient with a device needing to be consented and registered through a research-like process that's overseen by an IRB. The second point is how does liability shift as more people have visibility, more people and more institutions have visibility on this type of data? I don't have any answers, but these are important questions to consider.

This is a schema of the system that we're planning and hoping to implement at Children's, where we are taking data from devices, extracting them from cloud-based databases, from the manufacturer; we're taking patient data through mobile PROs, and we're taking clinical data from the EHR, integrating it into a database that has an application layer that then allows for a variety of functions, whether it's clinical surveillance, other clinical applications, research applications.

I have 30 seconds left, so I will not make my second point, which relates to the idea of sharing this information across systems to really provide that national level of safety and surveillance, and instead I'll skip to this, which is the idea that all medical devices can be abstracted to four components, and one of them is data storage and export. And I want to encourage all of us and our colleagues at the FDA to think about how we make that piece easier to update so that it doesn't lag behind the development of other data systems.

Thank you very much.

(Applause.)

DR. SILVERSTEIN: That was a quick focus on how we store and use data, so I

appreciate that.

Our next speaker is going to be Lia McNeely.

MS. McNEELY: As he said, my name is Lia McNeely. I'm a nurse practitioner and quality improvement advisor with the department of orthopedic surgery at the Children's Hospital Philadelphia. I don't have any slides.

The last time I spoke with Dr. Robert Campbell, the now late Dr. Robert Campbell, he asked me to join him at this meeting to comment on the use of clinical informatics to improve postmarket registries for surgically implanted orthopedic devices. For those of you familiar with Dr. Campbell, you know he spent a vast majority of his career as a champion for pediatric devices and his invention, the Vertical Expandable Prosthetic Titanium Rib, or VEPTR as we call it, has saved or improved the lives of thousands of children throughout the world who are afflicted with thoracic insufficiency as a consequence of childhood spine and rib deformity.

In order to understand the impact of a surgically implanted device on a pediatric patient, we need to be able to follow that patient serially prior to and sequentially after device implementation. Despite keeping a meticulous registry of this patient's procedure and complication, Dr. Campbell often stated that he never really had the data to show that his device improved the quality of life for patients treated with his device because he was not certain as to what was relevant to patients and families about their quality of life.

My job over the last year was to find ways to use the electronic health record to capture quality data on patients treated with the VEPTR specifically, and spinal growth modulation instrumentation in general, to find a way to move a real-world patient registry into the electronic health records that we could use as data for care management, quality improvement, and research, and to implement patient-reported outcomes measures clinically in this population.

As I set out to work on these projects, I realized that we needed to engage the one group that appears to be missing from this meeting here today, the electronic health record companies themselves who will provide this knowledge and think of themselves as data entry personnel, the EHRs that we interact with on a daily basis with an incredible amount of data on our patients that they could hold so much more.

As you've heard today, the electronic health record data is considered real-world data by the FDA, but this data may hold the key to future device development and device monitoring for our pediatric patients. Yet, for most pediatric clinical researchers, the data is only accessible through a costly chart review, and randomized controlled trial data is gathered outside of the electronic health record. Even at large institutions like CHOP, we are only beginning to get access to our clinical data from the electronic health record, and this requires the employment of a data analyst who's well versed in SQL coding.

I encourage the FDA and the other healthcare and industry leaders in the audience to open a conversation with the EHR companies to determine how those companies can work together to create data elements across the EHRs that will allow providers to capture data on pediatric diseases and devices, that will meet the standards of the FDA, and could be easily retrieved by clinician researchers. The creation of these universal data elements could facilitate the development and implementation of universal device registries that would benefit industry, the FDA postmarket monitoring system, and pediatric healthcare. In addition, the data generated from these registries could also be used to show insurance companies the benefits of these devices.

And to end, I will leave you with this: While Dr. Campbell felt he never had more than anecdotal evidence to show that his devices made a difference, at the viewing for Dr. Campbell last weekend, an orthopedic surgeon traveled from Japan to honor Dr. Campbell and thank his family for all of the Japanese children that Dr. Campbell had

helped with his pediatric device. Sorry, I'm trying really hard here. I'll note that if he had made it to this meeting today, Dr. Campbell would be thrilled to see the large group that is so invested in improving the number of pediatric devices developed in the years to come. Thank you.

(Applause.)

DR. SILVERSTEIN: Thank you very much, and it was a nice summary of what he contributed to the world of pediatrics.

Our next speaker is going to be Ilona Anderson, the Director of Clinical Research in Innsbruck, Austria.

DR. ANDERSON: All right, I want to just cover some of the barriers and solutions that we had while applying for devices with the FDA. Our company, we manufacture not in the U.S., okay? There are not many people here, but just to say we do get devices from other countries in the world. We have FDA approval from 12 months and above. We have the same device, software fitting, and indications for both children and adults. And I know someone said earlier that a child is not a little adult. There are some devices that actually work suitably for both groups.

As we provide data from the rest of the world, not in the U.S., we follow another guideline, and this is the ISO 14155, last produced in 2011. And here, children are included as a vulnerable population, and therefore, you should not study children and that you cannot prove the data with adults. And this is something we have today in all of our studies. This ISO will be in and is registered in the MDR, which is our EU law.

So we have issues with definition of a pediatric group. I was interested to see that most devices are for 18 and above, and that's often because you just need one or two subjects to get that approved. But we don't see that this definition is reflective of how devices can and should be used in medical practice and sometimes can be burdensome to

have this as a criterion to be addressed. And many devices can be used by all ages without restriction on performance or development, and perhaps this needs to be a discussion with the FDA of what is a pediatric.

We know that approval lags behind the rest of the world. We should be able to use this data to support pediatric use and should not have to use this to prove concept of new clinical data, and maybe the requirements should reflect this in a reasonable way, to use data from other markets and therefore not study in children.

We don't always need to prove in adults first. I've got 30 seconds, I know, but we would like to use proper use of the guidelines that are available. Sorry, it's just this doesn't work so quickly. We find the extrapolation barrier decision tree, sorry, the extrapolation decision tree is a barrier, and they do not always reflect the fact that, in our world, children are a vulnerable population, and they shouldn't be studied if data exists on their device use. So we should rather extrapolate this into the postmarket framework so that we follow the least burdensome approach with less strict selection criteria and looking more at clinical outcomes.

Our questions are ethical. Do you risk the development of a child for the want of a study or not? Thank you.

(Applause.)

DR. PEIRIS: I just want to take a moment to thank all the public comment speakers. We truly appreciate the opportunity to come to the FDA to hear about issues, concerns, especially those that we haven't had an opportunity to address in the comments that have been provided by our speakers or invited speakers. So thank you once again.

I did want to perhaps reflect on a point that was just brought up, both about EHRs and, you know, perhaps what was noted as the absence of specific companies. This is a topic that, again, we're very cognizant about and have been working on for a number of

years. Especially as we have been considering the development of NEST, we recognize that the data that is captured every single day in clinical medicine is very relevant, and we want to facilitate opportunities to work with EHR companies. Right now, the market is about two. There might be a few others that certainly are part of this, but those companies certainly can make a difference in allowing standardized data capture that can be aggregated and refined up to a level which might be considered regulatory grade, but it's certainly something that's important, so thank you.

And I also wanted to comment on the last speaker. Ilona, thank you once again for your comments and giving us perspective about how outside the U.S. the topic of pediatrics and pediatrics as a vulnerable population is considered, and I think it's very important, and the reason I bring it up is because one of the issues that we consider, and I think this might be reflected amongst many pediatric clinicians and the people that are doing pediatric clinical work and surgical work and interventional work every single day. If we continue to consider pediatrics as, what do I want to say, overly vulnerable, then perhaps we're unable to collect the data that we need in an appropriate and safe manner when we can. And I think we want to ensure that we're providing the right balance of ensuring that when something can be studied in children, that we're able to study it in children if it's done in a safe and appropriate manner. So, again, thank you for your comments. I appreciate it.

Our next portion of the agenda for today is the panel discussion, and I know it's been a long day. Thank you all for staying. We did not include any break time because I know everybody would be zealous to engage the panel. So I'm going to just take a quick show of hands. How many people would like a 5-minute break versus how many people would like to get started? So let's go with how many people would like a 5-minute break?

(Show of hands.)

DR. PEIRIS: All right. Doug, you were wrong. So what I'd like to do is go ahead and

invite all the panelists from the morning sessions and the afternoon sessions, if you can come up and take a seat, and while you're getting situated, I will try to do a little bit of a brief recap of things.

Today, what we've really heard from the beginning and earlier in the day is the fact that we absolutely need to consider the opportunities in terms of developing strategies for enhancing the ecosystem to develop devices for children. It's something that both industry and our clinical academic and AP partners feel is important, and I think that's what you've heard throughout the day. When we consider pediatrics, we recognize that pediatrics really is not just the medicine of, as I mentioned, well, childhood, it's in lollipops. It's not goo-goo, ga-ga medicine in a sense, which many people might conceive of and which we really want for all children to have that experience, that's perfect. But, again, everyone that recognizes and does work in clinical medicine in pediatrics every single day recognizes that we are pushing the envelope; we are making innovative changes and alternatives to the practice of medicine in pediatrics that influences the practice of medicine in many other areas, both in intervention, surgery, electrophysiology, imaging, and ambulatory sciences.

When we've moved into our evidence generation section, and this is going to be the key area that we'll be addressing today, we recognize that evidence generation is typically one of the most costly and time-consuming areas for getting a medical device to market. Infrastructure for evidence generation, some people might say, for adults is far better developed, and infrastructure for evidence generation in children still needs to be developed or has great potential to be developed. And we heard from a number of speakers today, including those that have provided support and grants by the FDA to help develop a global clinical trials infrastructure.

So I think the primary focus of the next hour, hour and a half, will be to begin to address the key issues in evidence generation, and we'll focus on that area today and

perhaps develop a few strategies. And tomorrow I'd like to keep the conversations a bit distinct. Tomorrow we'll be addressing the regulatory and economic issues. But I'll hand it over to Doug to start off with the first questions. Thank you.

DR. SILVERSTEIN: Okay, so the purpose of this panel discussion, I would look at it as sort of a way to wrap things up a little bit, bring some cohesion because there were so many different talks with so many great experts, and so to kind of make it a little easier for us to walk home today and say, okay, I think I know what direction we're going in and what we need to do.

So the first question is, and I think you've all heard a lot today, all the panelists, all the attendees, about nontraditional trial designs away from the RCT requirement and strategies to support evidence generation in pediatrics, and you've heard about NEST, modeling and simulation, real-world evidence. And so are these strategies for evidence generation going in the right direction to meet the needs of the pediatric community? And I want to focus on a couple of people and then maybe have the rest chime in, so I really want to start with Bob Kroslowitz, if you want to make a first comment, and then we can move on to others.

MR. KROSLOWITZ: Sure. I'd say, generally, yes. I think though, however, we are just starting to understand some of these approaches in the adult market and how, in the end, we'll be able to bring them into the pediatric space where there's sort of much fewer patients. I think that that will be something that we'll have to understand over time, but I think we'll need to see how this works out in the larger populations first. I think that some of the modeling and extrapolation, I think that, you know, with such small populations of patients, we'll have to sort of figure out how that's going to work.

DR. SILVERSTEIN: Thank you very much.

And I want to address to a couple of people. First, Barbara Christensen and also for

Steve Anderson, who have done some trial work, and I would like to know which of these trial designs have you used, and what challenges have you found for those designs?

MS. CHRISTENSEN: Well, I can talk about how the ACC has used registries in support of postmarket studies. And it was a collaboration with industry and the FDA around how a national prospective registry can be used to generate the evidence to support the continuing access and the postmarket studies. As I said, the data is captured as part of the course of normal clinical activities, and then that data can then be exported and shared for analysis and meeting the reporting requirements that industry has to the FDA. And we use that not only in the aortic TAVR space, but also in the implantable cardiac defibrillator space as well, and currently in the left atrial appendage occlusion.

DR. SILVERSTEIN: Um-hum.

MS. CHRISTENSEN: So for those different procedures.

DR. SILVERSTEIN: Thank you.

Steve?

MR. ANDERSON: I'd like to say that we have a lot of experience with this, but we really don't. In my previous company, I will say this, from an adult standpoint, the adaptive design, you know, using Bayesian statistics was challenging. It took months to come to agreement on how much to discount the priors; it was really difficult. And in my current company, which is pediatric specific, we've had the simple as possible design. These have been treatment only, experiential trials where really you're just trying to figure out if an instrument can be used. And so we really haven't gone into anything beyond the most rudimentary design, and even as I mentioned this morning, even with that simple clinical trial and doing a non-significant risk, it was challenging.

DR. SILVERSTEIN: Thank you.

I want to open this up to anybody who wants to answer the question. You've heard

a lot about some trial designs, but are there others that we all should be thinking about, including those of us at the FDA? We should be open to consideration of data evidence in other types of trial design? Does anybody have anything that leaps to mind and have any experiences with those?

DR. BERLINER: So my experience is in health technology assessment, and where I'm trying to (interrupted).

DR. PEIRIS: Elise, I don't want to interrupt you, but do you mind introducing yourself since you're new to the panel?

DR. SILVERSTEIN: Yeah, thank you.

DR. BERLINER: Sure, I'm Elise Berliner from the Agency for Healthcare Quality and Research, and I just want to say that working in health technology assessment, I am trying to look at all the evidence and put it together and really sort of help patients answer the question that was posed by patients like me. Given my current situation, what is the best possible outcome and how do I get there? So I'm really interested in how we can get the evidence to answer that question, and I heard a lot of things today, but I just wanted to put it together in maybe a different way.

So whether you are trying to use real-world data or randomized controlled trials, I want to emphasize what Juan and Lia said, two of the public commenters, about needing standardized clinical metrics and really integrating those metrics into the electronic health record and collecting it in the real world, because otherwise we're never going to be able to move forward with the evidence.

So we look at the PICO, the patients, interventions, comparators, and outcomes. So for the patients, we need standardized diagnostic criteria and information on patient characteristics. For the intervention or the comparator, we need those to be adequately described, so for the device, we need the UDI. For the comparator, the comparator could

be in an RCT, or it could be by looking at two different observational datasets, but we need that comparator to also be adequately described. So if it's a surgical procedure, we need details of the surgery. If it's a drug, we need to know what that is. If it's another device, we need the UDI. And for the outcomes, we need core outcome sets that have meaningful outcomes for patients, including quality of life.

And I think that when we had the discussion about collaborative communities, this is really, really important. So for people who are developing the devices, you really need to know who are the patients, what are the right outcomes to measure, what is the natural history of the disease, and until we have datasets that can answer these questions through standardized clinical metrics, then we're never, as a community, going to get anywhere.

DR. SILVERSTEIN: Thank you very much. You raised a lot of good points, and I'm glad you mentioned the patient-reported outcomes among them because I think that's an important point.

DR. PEIRIS: I was just going to hop in to give you some clarifying information. This is not intended to be a panel of Doug Silverstein asking each of the panelists different things. If any of these topics are of interest or if any of the audience members would like to step in, please feel free to come to the microphone and engage in the conversation. This is intended to be for all of us to learn, so thank you.

UNIDENTIFIED SPEAKER: Just quickly to that, though. So for those of us who are actually practicing clinicians, we have about 15 minutes to see a lot of our patients postoperatively, we're with a resident who may or may not glean the important facts, and then you have to try to get that data into an electronic medical record that when you review your notes, sometimes they're absolutely abysmal, you don't recognize that that clinic visit and encounter had nothing to do with what was reported. So it's coming up with the really efficient, almost menu-driven, sort of like my residents are always looking at this,

it's almost like checkboxes, you know, like that they could use to make this practical because otherwise it's not going to happen in that 15-minute encounter.

DR. BERLINER: Yeah. I mean, I think that I agree that that is what's really important, that's what the collaborative communities need to do, and the collaborative communities need to have patients and physicians and EHR vendors and people developing medical devices, and everyone has to come together and agree on an efficient set of standardized clinical metrics that can be feasibly measured in clinical practice consistently.

MS. TENENBAUM: Hi, I'm Cara Tenenbaum. I work at FDA. My background is in oncology, though, before this, and so, you know, as I think someone mentioned briefly COG, right, the Children's Oncology Group, earlier, and it's a huge percentage of children that are enrolled in oncology trials, and I don't think oncology is hurting for money. So I wonder if there isn't, you know, some bit of that model that we could take for the pediatric device space as well as we consider a lot of options in the future.

MR. KROSLOWITZ: I think that it's really, this is Bob Kroslowitz, difficult to extrapolate the drug experience to the device experience. I think you're talking, with devices, certainly much fewer patients, right? Our company is a standalone pediatric device company, and we treat 100 patients a year, right? So how do you know, that's a low number of patients to talk about and, you know, where the money comes from, right, it's not there.

I wonder and, you know, I thought about this a while, and I think we talked about this at one point, for really sort of small populations, very small pediatric populations and related specifically to devices, I wonder if we might explore some sort of alternative pathway of approval for, specifically for reimbursement reasons, right, so for a certain number of patients, maybe less than 100 patients, you're left with 50 patients where there is no other alternative device available. You might be able to do some sort of small

confirmatory study to prove effectiveness or performance of the device and then have some sort of conditional approval that would enable you to get reimbursement; however, you would have to go on, right, within a certain period of time, 6 months or a year, and be in either an HDE or PMA or another study to get, you know, prove efficacy and safety or probable benefit and safety, whichever path you decided to go, but would be able to have some sort of, you know, approval in the meantime that would enable you to get reimbursement for the device while you continued on to study the device.

DR. PEIRIS: Bob, thank you. We're certainly open to considering, within our regulatory framework, considering what types of options would work for populations like this. When we think about small populations, especially if there is a level of uncertainty that we have when we evaluate a device on the premarket end or the postmarket end, improving the level of maybe more certainty that we can have on the postmarket end once a device is released and being utilized and being able to clarify that information as we gather it and figure out whether that device truly is performing at the level that it's intended to is important. But concepts like that certainly need to be considered.

And you bring up the issue of reimbursement as well. You know, have the parallel review programs that are currently in effect to help sponsors clarify clinical endpoints that are both relevant to the regulatory agency, the FDA, and to the payers. So we should certainly have a conversation about how, perhaps, concepts like that could be worked into a regulatory paradigm for small populations, especially pediatrics. Populations like that may exist in adults as well.

MR. KROSLOWITZ: I was just advising, you know, you talked about the reimbursement, and this is a little bit off the topic, but briefly, I was advising another company, again, with a small population pediatric device that had started an early feasibility study, and we went to the clinical centers to contract with them to do the

studies, and the clinical contracting offices at the hospitals said you need to have CMS approval before we'll even talk to you. So we went to CMS, right, and we were on a hamster wheel; really, we were on a hamster wheel. We went to CMS, and CMS said the pediatric population is not under our purview; we're not going to rule. Go and talk to Medicaid. We went and talked to Medicaid, and Medicaid said we're not going to pay unless CMS rules.

DR. PEIRIS: I'll tell you on that specific topic, Bob, again, one of those areas that we're absolutely cognizant of. We are reaching out, through our innovation program, to engage Medicaid representatives so that we can begin to have a conversation on this.

MR. KROSLOWITZ: These are the big issues, though, right; these are the things that are obstacles, big obstacles.

DR. PEIRIS: Yeah, agree.

UNIDENTIFIED SPEAKER: Bob, what kind of conditional approval do you know of, that somebody would pay for something? CMS won't. Medicaid won't. And last time I checked, Blue Cross is not paying for anything that is conditionally approved. So I'm afraid that that doesn't make, I mean, I would like to know who's going to pay for something that is conditionally approved. Maybe you can elaborate on that.

MR. KROSLOWITZ: I don't know. What I was wondering is a conditional approval, is there some way that we could lobby for some reimbursement for the pediatric devices, especially for really rare orphan conditions. There's got to be some way that we can figure out how to do this.

DR. SILVERSTEIN: Go ahead.

DR. STRASBURGER: Yes, Janette Strasburger again. Along with what Bob said, I think that our experience with a new device and a new procedure is that we went to the AMA and the code committee, and we now have what's called a T code, it's a four-digit code, and

that code allows you to use an emerging device. Ours happens to be FDA approved, but the problem is that in order to go from a category 3 to a category 1, you have to have it used by lots of physicians in lots of centers, and that, for pediatrics, is very difficult, especially with emerging devices.

MR. KROSLOWITZ: In the state of Georgia, if you are a child enrolled in a clinical trial, Medicare will not pay anything. It doesn't matter what it is; if you're enrolled in any clinical trial, Medicare will not pay for your care in the state of Georgia.

DR. STRASBURGER: Um-hum.

MS. FEDERICI: Tara Federici with AdvaMed.

DR. SILVERSTEIN: Can you move the microphone, please, so we can hear you?

MS. FEDERICI: Can you hear me now?

DR. SILVERSTEIN: A little bit better.

MS. FEDERICI: Tara Federici with AdvaMed. I just want to respond to the comment from the gentleman. Yes, you're right, in today's environment, no one will pay for that. But I think what we're trying to do here today is come up with new ideas, new solutions that can be incorporated into a report to Congress. Congress has asked FDA to develop a report on barriers and solutions, and so we can all get behind new approaches, new solutions, and perhaps Congress can change the rules and we can have a situation where conditional approval could occur and be reimbursed as you continue to gather data. So I encourage folks to think proactively here today.

DR. PEIRIS: Thank you, Tara. And that actually gives me an opportunity to take it, maybe direct your attention to the slides that are up on the screens. These are the specific topics that Congress asked us to work on. As I mentioned at the very beginning of the day, many of these topics certainly do involve evidence generation, but we want to stay focused, as Tara said, on what types of solutions, what types of strategies could truly make a

difference, and what should we consider in terms of a summary report to Congress of what the public feels is most important in moving this field of pediatric medical device development forward.

UNIDENTIFIED SPEAKER: Following up on that, when we talk about networks, the focus so far has been on patient enrollment and even maybe some involvement of the local IRBs. But, in fact, the biggest hurdles are often outside of that scope. For example, the contracting that was mentioned earlier, contracting between either a manufacturer or even a sponsor with each individual hospital becomes an issue. These are the hurdles, you know, we can list a long list of hurdles, but these are the hurdles that are not covered by anybody but actually inhibit the actual conduct or at least the appetite of the sponsors from taking on these types of trials. So I think if we're going to look at this, we have to include or incorporate all of the hurdles that we don't normally talk about, and particularly in the network component.

DR. SILVERSTEIN: I think that's a good segue into our next question because we're going to be talking about research and infrastructure. So we've heard a lot about research and infrastructure today to help develop clinical evidence, but we also are aware that there's a less mature and robust infrastructure for pediatrics, I think, as a lot of you have been saying. So we understand that there is research networks and registries are part of the solution and not the entire solution, but we think about what are the major challenges of developing research networks and infrastructure in children's hospitals, and I'm going to address this specifically to Peter Margolis, Danny Benjamin, and Edward Connor. Any of the three of you can start off.

DR. MARGOLIS: Me, I'll start. So lots of barriers. One of the barriers that Barbara mentioned, when I talk to CEOs, they are very cognizant of the cost that they're incurring to maintain lots and lots of registries. Our current approach actually is mostly from the

perspective of the surgery or the procedure that's been done rather than from the patient's perspective, and that makes a registry much less useful for hospital CEOs, for clinicians who are trying to take care of patients, the last comment in the public commentary about the orthopedist who wanted to know what happened to his patient over time.

When we develop registries in those sort of vertical ways rather than following the path of the patient, I think we lose opportunities for making registries that are useful to the decisions that clinicians and patients need to make together, which don't happen at episodes in time but in today's world now involve a path that involves the care inside the hospital, outside the hospital, and at home. So I think we need to start to rethink the structure of our registries and orient them from the patient's perspective and the clinician's perspective. So that would be one starting comment.

DR. CONNOR: And I think that when we think about registries and underlying sort of platforms for doing clinical research and creating infrastructure, there really needs to be thought given to how those registries create product development readiness, which is not the same thing as doing research or creating a registry. So that element of product development readiness, which is the sort of thinking process that we've all talked about how to try to get through, it is really important to think about.

In our experience with a variety of different networks and registries and others, it's been that the conversations that go around the preparation for trials readiness or product development readiness actually informs a lot of the gaps that are needed in order to be able to answer questions about disease natural history or other elements of trials involvement that are really important. So that's one comment.

I think the other comment related to what was brought up recently is that just the infrastructure process of getting a trial started in an institution is dead weight; it's very burdensome. It's burdensome for the site, it's burdensome for the sponsors, it's

burdensome for everybody involved in the process, and so ways of reducing the physical operational burden at sites.

And, you know, it's particularly true for sites that are competent and qualified at doing this kind of research. Those sites get bombarded with lots of requests for doing things, and the challenge is that every individual sponsor and every individual program, whether it's drugs or devices or other elements, have their own unique proprietary ways of doing things, and many of those proprietary ways of doing things is really just business as usual; it's not really so proprietary. And we need to be able to get over those barriers and make a lot of those more standardized and realize that everybody's collecting in some ways the same kind of information. It's not really so proprietary methodology.

DR. SILVERSTEIN: What can we learn from the adults and how they set up? Not registries here, I'm talking about research infrastructure, what you were just talking about, Ed, about what can we learn from what adults have done to establish research infrastructure for clinical research? What have they done that we need to learn from?

MR. DEL MONTE: I'll jump in briefly. I think that last comment, it was incredibly powerful. I think if we can figure out a way to do some of this infrastructure building so that not every new product, every new sponsor is starting from scratch every single time, I think that can make a big difference, both in when folks are ready for a clinical trial certainly or are interested in novel clinical trial design but even way before that when we're still on the napkin with the big idea. And I think that the Pediatric Device Consortium have been so powerful in being that coach, that incubator or small business developer kind of idea that at touch points along the way, if you can reduce those barriers in small ways over a number of barriers, you can make a big difference. And so it would be really interesting to think through how to make those systems more effective.

Regarding registries, we have been looking at, at the Academy of Pediatrics for more

than a year now, the notion of registries and that we have tried to learn from organ systems and disease or condition registries or even drug registries that have been put together to monitor REMs, etc., and always in pediatric populations you're dealing with numbers problems, that the population is always small. And so what we have done, in fact, our board of directors, about a year ago now, made an investment in an exploration of whether or not the Academy of Pediatrics could produce a clinical data registry from a life course perspective. So could we take the aggregation of lots of different datasets, including patient-reported data, and put together a dataset that would actually be testable for all sorts of interesting questions but would not be specific to any one aspect of childhood or disease or condition or organ but across social determinants of health and all the other things that impact the health of a child?

So we are about 6 or 8 months or so into that feasibility phase. We've made some significant investments in doing that, and so we're going to give it a try. And so I just want to invite everybody who's interested in partnering in some endeavor like that to be a part of what AAP is doing. If we can figure out how to get a registry of registries, a larger dataset, I guess the term "big data" is now out of vogue, but it was really hot for a while. The notion is to think about that because it's a scale problem in pediatrics; it always is. And so if you're looking for a signal that's washed out among lots of others, we're going to need to do that. But I can't think of any other easy way to aggregate data in such a way that you could get questions answered.

DR. MAHER: Mark, I agree, but I think it's sort of thinking big, and if you think about the electronic medical record was, now it's just sort of how we practice medicine, but that was a stroke of a pen that really changed that, and I think it's going to take the federal government, but involvement of many of the people here at the FDA and the AAP and many others, but really a national database, a registry for children is really what I think needs to

be on the table.

And there has been discussion with a lot of the senior vice presidents of IT at pediatric institutions with some of the major EHR, mostly Epic and Cerner, and they're not ready to, you know, work with each other. But Epic is sort of the big, big player so far as pediatric EMR, and they are in reasonable discussions with how to be able to put that together and have a cloud-based database for children, and then all the registries can be sort of subsets of that.

MR. MATLIS: So just one (interrupted).

DR. SILVERSTEIN: Just introduce yourself quickly, please.

MR. MATLIS: Sorry. Dan Matlis with Axendia. So to build on what Dr. Maher just said, just hot off the press is Amazon, IBM, Microsoft, well, the two other very large companies just at the White House announced that they're going to reduce friction around electronic health record systems that are built on the cloud using artificial intelligence. So the technology piece, in a way, is the easy part today. Today, the problem is not technology. When I started working and we'd try to integrate systems, there was token ring, and token didn't go around the ring fast enough. Now technology is not the issue.

Where you asked about what can we learn from the adults, I've been involved in the Case for Quality initiative working with Francisco Vicenty, and we're having the same exact issues with adults. I'm in the product quality outcomes analytics team, right? So the intent is to find out what the outcomes are for using these devices, and the two products that we picked were endoscopes and mesh. There's plenty of data. The problem is nobody's willing to share because there are legal issues associated with sharing. So what we really need to change is the culture. It's not the data, it's not the technology; it's the culture. We need to be willing to share, and we need to be willing to take some risk for the benefit of everybody rather than be protective about our data.

DR. MARGOLIS: I actually think that's clear; pediatrics is ahead of adults. So one of the things that we've observed in multiple networks now is that when you start with patients and clinicians, you actually can get to agreement about what the important outcomes are and tremendous amounts of sharing. If you take the solutions for Patient Safety Network as a primary example, that's the most sensitive data that there is from hospitals.

MR. MATLIS: Um-hum.

DR. MARGOLIS: A hundred and thirty hospital CEOs have agreed not to compete on safety of patients.

MR. MATLIS: Yeah.

DR. MARGOLIS: And they're sharing their data transparently with one another. It happens on a daily basis.

MR. MATLIS: Yeah.

DR. MARGOLIS: So there are multiple networks that have now formed in this way and where we are demonstrating in pediatrics that we can overcome these problems, and I think, like I said, that we're ahead of adults.

MR. MATLIS: But we need to also bring to the table the payers; we need to bring to the table the manufacturers. All the constituents need to be willing to share for the greater good, and that is a culture change and a big challenge.

DR. SNYDER: Brian Snyder again. Just to comment. So there's been a lot of focus on the medical record, natural, real clinical data. On the flip side, I represent pediatric orthopedics to the ASTM, which comes up with the bench tests that often FDA and other people will defer to in terms of trying to establish safety. One of the problems at the ASTM level is we don't have appropriate tests that reflect pediatric devices. In other words, a lot of the bench tests that were developed really are for adult disease or, at best, surrogates,

and it's going to be really important to be able to use real patient data to help inform what are the modes of failure and what tests should be developed as bench tests that industry can then use as the benchmark to establish safety that the FDA can refer to.

DR. PEIRIS: And just to follow up on that, the talk that Leonardo gave certainly helped highlight the fact that our Office of Science and Engineering Laboratories are certainly looking at those types of testing modalities.

UNIDENTIFIED SPEAKER: Okay, a comment over here.

DR. SILVERSTEIN: Oh, sorry.

UNIDENTIFIED SPEAKER: No, no problem. Just a quick comment on the previous comment before this one about the legal aspects. Perhaps a good place to look for a legal framework for data access is automobile crashes and specifically event data recorders, these black boxes that are now ubiquitous in all our automobiles. Those data are available for research, and there was a lot of arguments about does the customer own the data or does the public own the data, and the feds actually have rights to those data and use them without a barrier in a de-identified way. Just a comment.

DR. SILVERSTEIN: We started talking about research networks, and I think we kind of meandered over to registries, and we kind of did them together, which I think makes a lot of sense. But I guess I want to go back to a question for those who have developed a research infrastructure, and I guess what has always puzzled me is if you have all these children's hospitals around the country, some small, some medium, some large, why we are not using a model for research infrastructure that exists at certain very successful hospitals and why the other hospitals and the other hospital systems are not reaching out to them to get advice basically as a consultation.

Within my world of pediatric nephrology, a lot of us, when we're developing a dialysis program, we consult with those around the country. I did that in my past and

including when I was at Children's National and just to try to get some more information about how is the best way to run a program, whether it be the literal structure in terms of what facility do you need, etc., or how do you run your monthly meetings, that kind of thing.

And so is that being done in pediatrics? Are we using each other as resources to understand how we need to build something or is, because you mentioned the research infrastructure is different, and to me, that's frustrating because why aren't we working with each other so we have not just a uniform one but an optimal research infrastructure within each facility and so they can talk better to each other but also become better?

DR. CONNOR: That's exactly what we're trying to do, and we're moving forward on the notion that a lot of us have done large clinical trials and very small and complex orphan drug trials. Understand that there's a set of needs of pediatric centers, and those set of needs are partly mechanics, they're process and that sort of stuff, improvement, but a lot of it is the sort of peer-to-peer interaction that allows problems to be solved over time, so actually working with the Anderson Center and others as part of IAC to actually foster that as part of the infrastructure development.

You know, the ecosystem that's going to be doing trials is a diverse heterogeneity. Some folks, some hospitals are really great. Some registries and centers are really great. Some foundations really know a lot about trials, and some know very little about trials. And the leveraging of the information around trial design and efficiency and things that work and best practices are often lost because we keep reinventing the wheel all the time with these networks.

So the goal of IAC, as we launched it, was really to be not in charge of those things but a home for that common sort of knowledge that actually is in many ways common among small studies, large studies, device studies, drug studies, registry, and postmarketing

studies. And I think we need to really, the long-term success is going to be not to have to relearn that every time that we do a new initiative.

DR. SILVERSTEIN: Thank you. And I'm just going to actually reach out to Kurt Newman and Dennis Lund because I wanted to know what your centers, one that I'm very familiar with and one that I'm not, are doing exactly of what we just heard about.

DR. NEWMAN: Well, thank you. I think when you've seen one children's hospital, you've seen one children's hospital, and the ecosystem in each center can vary widely depending on the university relationships, which frequently, for many children's hospitals, is the real driver to research as opposed to, and when you look at the spectrum of children's hospitals, there's 35 independent, locally governed, standalone children's hospitals. There's probably 200 other children's hospitals within adult health systems.

DR. SILVERSTEIN: Um-hum.

DR. NEWMAN: So there's frequently lots of tensions that crosscut many things. I think the thing I'm most optimistic about is the maturation of the research enterprises in these children's hospitals, and I think Peter and his work is the perfect demonstration of how these hospitals are overcoming, in some cases, competitive situations to look at what's best for the patient, and let's focus research questions on that, and something as sensitive as adverse effects or bad outcomes or whatever, where you have people coming together. So I'm really optimistic, and I think the resources that are being generated, the studies being done. The other thing is the philanthropy that is really being mobilized around a lot of these questions.

This conference, you know, wouldn't have happened even 5 years ago, so when you look at the attendance here and the interest, so I'm very bullish on the ability of the children's hospitals to be a primary driver on this agenda. And if you look at what's happening at Children's Hospital of Philadelphia, Boston Children's, Cincinnati, L.A., they're

all here. Stanford. There's big interest, and in their own way, they're mobilizing around innovation and creativity. And so it can be frustrating because the pace isn't fast enough, but I think the passion and commitment is there.

DR. PEIRIS: So I don't know if anybody caught on, and Danny, I'll give it to you in a second, but part of the reason that we put together the talks from Dr. Tarver regarding our strategic priority and collaborative communities and had Dr. Lund speak right after was to clarify that connection. There is potentially a huge untapped resource with respect to pediatric academic medical centers and, as Dr. Newman mentioned, other medical centers that have pediatric expertise across the country, and perhaps they would be a great convener of a collaborative community to really address many of the issues that we're discussing here.

Danny, I'll hand it over to you again.

DR. LUND: Thank you. Well, I certainly second what Dr. Newman has said, and I think that the children's hospitals do have a great opportunity here, and a lot of it tends to be kind of problem-specific or problem-driven. So if you look in the latest, hottest areas of research advancement now, immunotherapy, gene therapy, the children's hospitals are actually developing collaboratives around these particular problems and are really working together on this. And, again, it goes back to the fact that we have a problem of scale in pediatrics and that we're only going to solve these problems if we can aggregate enough patients to have meaningful data.

I think devices present a little bit different problem because fundamentally the device play has been very entrepreneur. And so, you know, one device I'm thinking of that we're developing at Stanford right now, the clinical trial to do proof of principle is going to cost $20,000 a patient. Well, the likelihood of having an impact on a large number of patients, you know, this may help, at most, 100 patients or 150 patients. It's going to be

pretty hard to find anybody besides a philanthropist or a hospital to fund that kind of a trial. And so how do we again get together and not only marshal our data but actually marshal our resources to solve some of these kinds of problems?

MR. KROSLOWITZ: I just wanted to make a comment. So we've recently been engaged with one of the learning networks, and specifically, in the cardiovascular space, it's the Action Network that's being driven by folks right now in Cincinnati and at Stanford, and it's really the clinicians that have gotten together and organized this learning network and have done really a tremendous job and are really, really engaged. And I think that this is something that has the potential to really bring all of these sort of groups together and make a difference and, you know, provide real-world data for devices moving forward, but also to help each other, right, to figure things out. And it's tremendous, the collaboration that we're seeing across centers and some of these learning networks. I think that's something that's going to be important, moving forward.

DR. SILVERSTEIN: Very encouraging.

Shuvo Roy.

DR. ROY: Yeah, Shuvo Roy from UCSF Pediatric Device Consortium. Building off on the hospital system, so we have an FDA-supported pediatric device consortium at our place, but we've expanded that with engineering for Children's Health Initiative that we try to bring people from around the Bay Area and eventually across the country to develop ideas, bring different people together to advance the development of children's pediatric devices.

We had a symposium last year, and we had one this year, and we'll have one next year. But for many of the developers, there are two areas where we think, at UCSF, we can provide a benefit, giving access to key opinion leaders in the children's health space; we are willing to do that. You want a way to engage with the supply chain entry. Our institution is willing to do that. So I hope the other hospitals can also participate in those kinds of ways.

And we also have a small grants program that's partially from the FDA but also outside of the FDA that support the development of devices that gets the devices towards clinical trials. So these are some of the things we are doing, and hopefully, other health systems may be doing the same thing.

DR. SILVERSTEIN: Okay, I wanted to just circle back a little bit. We talked a little bit about registries, and we kind of went in and out. I wanted to explore that a little bit more; we heard a lot about that.

And, Rachel, I wanted to know if you can provide some comments to us about you had a lot of success with NEST, and it sounds like you have a couple of those programs that are going to include pediatrics. So from your experience, what makes registries successful, and what can we learn from the registries you've been involved with, and how can that bring different groups of people together?

MS. RATH: Sure. Unfortunately, our test cases are just launching now, so what we're hoping to learn over the next few months, and the test cases are all very quick projects, so we're delving into that beautiful contracting phase right now, but we are expecting results and lessons learned from these test cases by as early as May of 2019, and these test cases use a variety of real-world data sources, so some of them do use the registries. The majority of the registries participating are tied to MDEpiNet, so we are really excited to see, in these test cases, what are the strengths of the registries, what are the strengths of the real-world data coming from outside the registries as well. So that's something that hopefully, in the next, you know, 6 to 9 months we'll really be able to delve into much deeper.

DR. SILVERSTEIN: So what principles did you use or what factors did you consider when you were trying to figure out which is the best registry to set up? And how did you determine what's the predictor or the measure of success for those as you go forward?

MS. RATH: Those are great questions. So lot of this will be certainly set by the data quality subcommittee as we move forward. The initial set of data collaborators, network collaborators that came into the fold, where a lot of them have ties to PCORnet where they have very rigorous data quality checks in place, and then, additionally, the MDEpiNet registry came to the table as well. As we move forward with the data quality subcommittee, they will be putting data quality standards in place that will mostly apply to our existing network collaborators but then also look at new network collaborators that are coming in. So we're hoping to envision a very transparent system where you can see the data quality of each of our network collaborator sources.

DR. SILVERSTEIN: That's terrific. I want to reach out to the audience. Does anybody have comments either about research infrastructure or registries?

(No response.)

DR. SILVERSTEIN: Anybody else on the panel?

DR. BERLINER: Yeah. So for those of you who don't know, AHRQ has a book on how to do a registry, the AHRQ registries handbook, and we have a checklist of best practices in there that could help inform that question of what makes a good registry.

And I just wanted to make two other comments: One is somebody made a comment before about whether it's efficient to have so many different registries on the same topic and especially when there's such a small patient population. And so, again, I just want to get back to that issue of having standardized clinical metrics and core data elements because then data could be analyzed across registries. So it's not so much a question of just having one registry; we just need to have common data elements across systems so that we can analyze data across systems.

And the other thing about registries, and in general, the pediatric populations you're talking about here is that it seems to me that it's very analogous to rare genetic diseases in

pediatric populations, and there are really engaged patient-parent communities who are working on developing registries for these populations, and they're sharing methods together with NCATS at NIH, which has a program to help rare disease registries. And I think the pediatric device community should be partnering with those groups and also with the parts of FDA that are approving drugs for these rare pediatric diseases.

DR. SILVERSTEIN: Thank you.

DR. ESPINOZA: I think another way that we might be able to advance some of these, particularly related to registries, is in developing a core set of data tools, so whether those are ETLs, standardized ETLs, extract, transform, and load protocols, to go from one format to another, particularly from EMRs or other data sources into some standardized data model that has an existing data dictionary that has been pre-agreed upon by a panel of experts, but those kinds of reusable tools that could be hosted on the web and anybody could download are really helpful. We've had some good experience with, we are part of, CHLA, we're part of a working group of Cerner-based institutions that all are working in OMOP as a common data model, and there is a hub site, and everybody has their tools loaded up in terms of transformation and normalization of data, and that kind of resource that can be centrally supported and centrally guided, I think it's something that can help advance registries and research from devices.

DR. SILVERSTEIN: Thank you.

I'm going to go ahead, sure.

DR. LUND: Just a quick comment. You know, I think we've talked about registries, and you know, Kurt Newman and I, as hospital CEOs, literally are pulling out our hair about registries because we have so many registries and we spend so much money on registries at children's hospitals. I guess one thing I think that is a real step in the right direction is there are CMS administrators, Seema Verma has really come out strongly in favor of EHR

interoperability and whether it's going to be HL7 FHIR or some other platform, but we have the ultimately registry; it's called the electronic health record.

DR. SILVERSTEIN: Um-hum, um-hum.

DR. LUND: And we just have to figure out how to get them all to talk together and how to mine them properly.

DR. SILVERSTEIN: Yeah.

DR. BENJAMIN: Yeah, I think that's actually an excellent point, and not the idea, but the concept of common core data elements are really important in that exercise. It is sort of, you know, a deadly boring project often to deal with those very mundane but core elements that are necessary for trials development, and at the end of the day, whether it's modeling with disease progression, it looks like, or fit-for-purpose sort of tools that you can use in product development, it always ends up being a discussion about whether or not those things are present and the advantage of having core data elements as part of the process.

DR. CHRISTENSEN: And I'll just say that that's the ultimate goal, right, is that it's seamless and that big data can be extracted out of the EHR and used for multiple purposes, right? Capture it once; use it multiple times for multiple things. That's great. You give up a little bit of the quality piece, so there's tradeoffs. You can get a whole lot of data, but is the quality where you need it to be? And in some cases it might be perfectly fine. It depends on the questions you're trying to answer and what you're trying to do. But I think it's mind-numbing sometimes, the work that it takes to do that. But I think we're making some progress, but probably not as quickly as we'd all like.

DR. BENJAMIN: I think there are examples of where, which are good use examples of how those things can actually be extraordinarily productive, and I think the more we can find the sort of ready for primetime examples of how you can take that data and use it for

regulatory purposes and for informing, you know, fit-for-purpose sort of tools for product development, the better off we'll be. So there's one exercise, which is the global exercise of we have to do it for everything, and there's another exercise of having really good examples to lead the way in how to do it well, and often, people follow after that because they want to build on success.

DR. CHRISTENSEN: I mean, I'll just give you one example. We captured hemoglobin A1c in our outpatient registry. We had close to almost 900 different ways that people would put hemoglobin A1c. You'd get "$c1." You know, it's just amazing what you see. So yeah, conceptually. But there has to be some rules around how things look, yeah.

DR. BENJAMIN: Well, somebody did some assessments recently, I think NICHD folks, at some level about how many ways is a child classified in various federal and other systems of what a child is called, and what age groups childs are, and everybody has the definition that they use, but if you're the clinical person or the person trying to use that data, the sort of irrationality of having multiple definitions of even what a child is, is what we're starting with very often.

MR. KROSLOWITZ: These issues, though, were addressed in registries and in clinical trial databases, so there must be some way, right, to address them in the HER, and imagine, imagine the cost savings in resources alone, right, of not having to have people sitting around entering the data here, entering the data here, and the savings on the registry cost of these registries, I mean, would be tremendous. It would make a tremendous impact in the cost of doing research.

DR. BERLINER: So I just want to mention that the Pew Charitable Trust is working on this, and they're going to be having a meeting in a couple of weeks, so if anyone's interested, you know, you might want to check that out, and you know, I think that they would be interested to hear that this community is interested in a use case also.

DR. SILVERSTEIN: Yes.

MS. McNEELY: Thank you to everyone on this panel for taking up this topic. One of the things, as a provider and also as an educator, that I have learned through my experience over the last 10 years working with patients and working very heavily with the EHR system at our hospital is that we also have to reeducate and start to think about how we educate our medical staff and our medical providers on the importance of what they're putting into the EHR. Back in the days, we used to try to convince surgeons to actually print nicely so we could read their documentation; now it's about making sure that the information going into the EHR is reasonable and reliable and it's received, Barbara was mentioning that we're not putting in blood pressures and we're not putting in things 800 different ways. And that is an educational piece that I think, actually, if we embed that in our medical school curriculums and everything else, we might actually see some benefit down the road as well.

DR. SILVERSTEIN: Okay, so thank you very much. And we did get into a couple of topics that we didn't want to talk about, but I think it was worthwhile to let these things go a little bit further. We didn't talk about extrapolation, but I think you heard a lot about that today, and the collaborative communities, which Michelle led off with, and we heard a lot about that along the way.

So I want to thank our panel for a great discussion. I think there's a lot more to talk about, there's a lot more to think about, but certainly we have some information we can provide the Congress and some feedback. So I want to also thank the people here at the FDA, in the audience, and those on the phone, on the Webex and also anybody who called in along the way. And, finally, I just want to say, to our staff who is sitting over there, they're not listening to me.

(Laughter.)

DR. SILVERSTEIN: No, I want to thank them.

(Applause.)

DR. SILVERSTEIN: I'm sure Vasum was going to do this, but I just said if I don't do it, you know, I'll kick myself. They did a great job in just keeping everything going, and I'm just very thankful for the contribution that they have made here today; it would not have happened without them.

So thank you very much. Get some rest. Don't think about any of this until tomorrow morning so we have fresh minds, and we look forward to seeing you all tomorrow morning.

DR. PEIRIS: And we start tomorrow morning at 8:30. Not 9:00, 8:30. Thank you.

(Whereupon, at 5:28 p.m., the meeting was continued, to resume the next day, Tuesday, August 14, 2018, at 8:30 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PEDIATRIC MEDICAL DEVICE DEVELOPMENT

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Silver Spring, Maryland

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SHAYLAH LYNN BURRILL

Official Reporter