Integrating Clinical Studies Into Health Care Delivery: Post-Market Evidence Generation for Medical Products
Virtual Public Meeting
November 14, 2023 | 3:30-5pm (Eastern)

Transcript

Welcome & Opening Remarks
Susan Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (00:00:01):

Hello, and welcome to our virtual public meeting, "Integrating Clinical Studies Into Healthcare Delivery: Post-Market Evidence Generation for Medical Products." I am Susan Winckler, and I have the honor of serving as the Chief Executive Officer of the Reagan-Udall Foundation for the FDA. As we kick off this meeting, we are releasing our newest report, "Enhancing Post-Market Evidence Generation for Medical Products."

(00:00:24):

We will spend the next 90 minutes discussing the need for integrating clinical studies into healthcare and review, at a high level, the report's recommendations to help FDA and other stakeholders better facilitate and support post-market evidence-generation studies that answer clinically meaningful questions and address gaps in clinical evidence. You can find our full report with its 30 recommendations on our website at reaganudall.org. So let's talk a little bit about our agenda.

(00:00:55):

In just a moment, we will begin our first discussion of the day with a panel exploring patient and provider perspective on the need to better integrate clinical research with healthcare delivery, or the 'why' the foundation convened an expert panel to generate this report. Then, we will hear directly from panel members in a top-line exploration of key recommendations and themes in the report. Finally, FDA Commissioner Califf, who requested this report, will share his thoughts on the importance of evidence generation and how it can be supported in the context of healthcare delivery.

(00:01:31):

The full agenda and brief bios of our speakers are available on the foundation website, and a link is posted there in the chat window as well. So to get us started, I am pleased to welcome Dr. David Fajgenbaum, who, in addition to his role at the University of Pennsylvania School of Medicine, is a member of the Foundation Board of Directors and founder of Every Cure. Dr. Fajgenbaum, would you take the role of moderating our first panel, grounding us in the need to better integrate clinical research into healthcare delivery?

The Need for Post-Market Evidence Generation: Patient and Provider Perspectives

Moderator: David C. Fajgenbaum, MD, MBA, MSc, FCPP, Univ. of Penn School of Medicine
Wanda Brisbane, The 4 Winds Services, Inc.
Samuel Brown, MD, Intermountain Health
Jennifer Byrne, Javara Research
Ramita Tandon, Walgreens Boots Alliance

Dr. David Fajgenbaum (00:02:03):

Absolutely. Susan, thank you so much for the introduction and for giving the opportunity to moderate this session, which, as you know, is very personal for me. In fact, I'm alive thanks to post-approval evidence generation. As a third year medical student, I became critically ill with a deadly disease called idiopathic multicentric Castleman disease and spent months hospitalized in the ICU. I even had my last rights read to me because my doctors didn't think that I'd survive. I was eventually started on a clinical trial drug that, unfortunately, did not work for me, but I was given a combination of seven chemotherapies that did work and got me into remission.

(00:02:41):

But unfortunately, I continued to have relapse after relapse. I knew that my only hope would be to identify an existing drug that was already in the market for something else that maybe we could repurpose for me. See, I knew that was possible because many diseases share the same underlying problems and can, therefore, be treated with the same drugs. And there are many famous examples – drugs like thalidomide that were first approved for leprosy and then utilized effectively for multiplemyeloma, or Viagra, which we all know it's typical first use, but it actually also is a lifesaving drug for pulmonary arterial hypertension.

(00:03:14):

And so for me, having failed to respond to the only clinical trial drug and having a deadly disease that was going to continue to relapse, my only chance would be to generate evidence around existing drugs on the market to maybe be able to identify an existing drug that could save my life. So I began storing blood samples myself. And during my fifth relapse, I got the same combination of seven chemotherapies again that weren't made for my disease but were repurposed for my disease.

(00:03:40):

And when I got out of the hospital, I went to those same blood samples and performed experiments on them that uncovered that a key communication line called mTOR was highly activated in my samples, and I thought that maybe an mTOR inhibitor already on the market could maybe be used to save my life. Importantly, I turned to some existing evidence that have been generated around that mTOR inhibitor called Sirolimus, and it's use in another disease called autoimmune lymphoproliferative syndrome. I utilized the same dose that was used in ALPS in my case as the first patient ever with my disease to be treated with Sirolimus and have now been in remission for over nine years.

(00:04:17):

I've launched a center here at the University of Pennsylvania to continue to perform this sort of deep immune profiling and then look for existing drugs that can be repurposed, that we can generate more evidence around. We've also performed a number of post-market evidence generation studies, including real-world evidence and also clinical trials, including a clinical trial of that drug I mentioned earlier, Sirolimus, for my disease, which is saving my life. So you can imagine that over the last nine and a half years, I've been laser-focused in this idea of generating evidence to unlock additional uses for drugs.

(00:04:48):

And through our center here at Penn, we've identified and advanced 16 more drugs that are on the market for one use to be used in an additional disease that they were not initially intended for. And so you can imagine why I'm so excited about this report that the Reagan-Udall Foundation has put together. And just to sort of frame where we are, amazingly, humankind has developed 3000 FDA-approved drugs that are approved for about 3000 diseases. Now, the average one of those drugs is approved for about two to three different diseases, but many of those diseases that have an approved drug also have two to three drugs approved for them. So we need to generate more evidence around those 3000 drugs for the 3000 diseases that they're indicated for.

(00:05:32):

But there's also another 9,000 plus diseases that don't have a single FDA-approved therapy. And in many cases, there's evidence that would suggest that maybe they could actually be repurposed and reused in new ways, again through generating evidence to unlock these insights. One year ago, I launched a separate nonprofit organization called Every Cure to leverage the power of artificial intelligence on the world's biomedical knowledge to create a system that systematically identifies and prioritizes the most promising opportunities for using drugs and diseases that are different from what they were intended for to help us to prioritize which drugs for which diseases should have further evidence generated.

(00:06:12):

So as we read in today's report that came up from Reagan-Udall Foundation and was requested by Commissioner Califf, more work is needed with regards to evidence generation. The system is inefficient with regards to data flow. Physicians and patients are not engaged [inaudible 00:06:28] at the level that we need to be, and data-sharing hurdles are just completely slowing progress. So for anyone who's read the report, you'll be pleased to see that there are 30 recommendations. Really in-depth work was done to figure out how we overcome these hurdles. And we've assembled what I think is a really great panel to share about what's the current state of evidence generation and to highlight some of the challenges that exist to really frame the next part of today's session.

(00:06:53):

So now I'd like to spend some time with some of these other panelists, chatting about a few other perspectives and also experiences with regard to post-market evidence generation. So let me start by first turning to Dr. Samuel Brown. Dr. Brown, it's good to see you again. Dr. Brown is a pulmonary intensivist by training who currently serves as vice president for research and as research professor at Intermountain Health, a nonprofit healthcare system, the Intermountain West region of the United States. Dr. Brown, by overseeing research at a large academic health system, you found ways to incorporate post-market evidence generation into practice. What are the benefits that you've seen, and how has it improved your healthcare system?

Dr. Samuel Brown (00:07:33):

Yeah, thanks, Dave. It's good to be with you. And I'll step back just a tiny bit to think about what we are after as a health system. We have a core academic medical center, and then we have a large portfolio of hospitals and care sites that provide integrated care for a large number of people across seven states. And as I've been thinking about the role of health systems in this question, it seems to me that our key strength is our relationship with the communities we serve, and trust is really the bedrock of that relationship. They trust that with high fidelity, we will provide them top-notch care according to current standards.

(00:08:15):

And they trust that we will find and offer the top-notch care of the future and that they trust in the process of doing this that their well-being is our top priority. And as health systems, we have distinctive perspectives. They do not expect us to do bench research, and we don't do bench research. Registration trials, we make sure to have a large pipeline of those for people who are not well served by usual care that need safe access to the most promising experimental therapeutics. What they really expect of us is that we are constantly learning and then implementing the best approaches to therapy.

(00:08:54):

And for Intermountain, this has been particularly true as we have leaned in, I think, more than anyone else in the country. Don't quote me for sure, but that's the sense I get into the question of value. In other words, our goal is to receive the financial resources we need to take care of patients in the future through doing best by patients in the present. So rather than the fee-for-service model where whatever we do, we get paid for, and isn't that great, we really do want to be maximizing their health as best we can.

(00:09:30):

And as we've worked on this, it's clear to us that even where randomization is used to limit bias, the work that we're fundamentally concerned with, again outside of the registration trial portfolio, is fundamentally clinical care. And that means that some of the regulatory infrastructure, not just at the agency, but also with OCR and OHRP and others, sometimes feels like it's not appropriately responsive to the needs of comparative effectiveness research or the next-generation learning health system work that we want to do because we are interested absolutely in finding new therapies in the repurposed agent armamentarium that will help our patients and optimize their health.

(00:10:17):

But we also want to know which of the available approved, even on-label applications of medications is going to bring the most value to the communities that we serve. So as we're thinking about the next generation of post-marketing evidence generation, it's important to us that we be thoughtful about bias minimization and that we be thoughtful about constraints that come from a variety of regulatory agencies that may inadvertently treat fundamentally clinical activities as if they were awfully similar to registration trials. And then just the closing thought is healthcare's changed a lot in the last few years, and it used to be the case that we in the health systems and the academic medical centers could subsidize a lot of this research work off clinical margins.

(00:11:13):

But the reality is that clinical margins are getting smaller and smaller, and it's becoming less and less practical for us to subsidize these kinds of activities off clinical margins, which means we're going to need help from the broader community of regulators and industry partners to figure out ways to fund and support and implement this kind of evidence generation that builds trust with the communities we serve. So we have to be very thoughtful about conflicts of interest and about perceptions that stockholder duties are in conflict with the duty to care. And we need to be mindful that for us to carry forward this pragmatic evidence generation, running them on INDs is a guarantee that they won't succeed.

(00:12:02):

It's making us so safe we can't actually do our jobs if that makes sense. So what we are trying to think about in the health systems is, at this point, how do we partner with industry and regulators in a way that maintains trust, that manages their financial resources in a way that makes it possible for us to be ready to serve future patients as we serve current patients and is mindful of the infrastructural needs. It's very difficult for health systems to do intermittent one-offs. It's hard to just get those into these tight

clinical margins. So infrastructure, arms-length relationships, and collaborations that minimize regulatory obstacles to these kinds of trials, I think, would be of great use to us in the health systems and the communities we serve. Thanks.

Dr. David Fajgenbaum (00:12:50):

Yeah. Well, thank you so much, Dr. Brown, and I love your initial comments around trust. And I think that's just so fundamental to everything that we've been chatting on that we're going to continue chat about today. Great. Well, let me turn it over to Ms. Tandon. So just continue to think about clinical studies in healthcare settings. I'm really excited to introduce Ramita Tandon, Chief Clinical Trials Officer at Walgreens Health, where she leads the growth for new clinical trials business. Ms. Tandon, what is it like to conduct offsite decentralized trials outside of a hospital or clinical setting like Dr. Brown was speaking to?

Ramita Tandon (00:13:25):

Thank you, Dr. Fajgenbaum, for having me, and good to be here with my colleagues. Just to step back a little bit around Walgreens and what we're doing as we are moving into healthcare, and we're on this considerable transformation as we leverage our physical footprint. We've got 9,000 stores and pharmacies across the nation. We serve roughly around a hundred to 110 million what I call citizens across this nation. And we learned a lot during the pandemic. And for us, it was we quickly learned it was not a one-stop shop in terms of strategy as we delivered the vaccinations across the communities that we serve. And we recognize that almost 40% of our locations are in underserved communities and communities of color.

(00:14:14):

And so, as we think about the clinical trials enterprise, we were very focused on creating an enterprise here at Walgreens that would ensure inclusivity, accessibility, and finding the best way or creating the right highway as we bring trials into our locations. So in the last 18 months, we've certainly activated a number of our locations to become clinical trial centers. Now, these centers are mainly, first and foremost, our welcome entry hubs. Every day roughly, we have about eight to 9 million citizens that come to our stores and pharmacies. And so, at many of our designated locations, it offers an opportunity for consumers and patients to come into these locations and learn about what a clinical trial is. A lion's share of our nation do not even know what a clinical trial is, the mechanics of participating.

(00:15:14):

So there's a lot of foundational awareness and education that's happening at these clinical trial hubs. And then, as we progressed in the journey, we have a number of trials underway, including leveraging our physical footprint where patients can come in for low-complex services, whether it's screening, diagnostics, or lab draws. And what we're finding as we're implementing these programs, it's proving to be quite accessible, right. We're giving it an opportunity for patients who, traditionally, one, have never been invited or don't even know about a clinical trial to be able to come in, learn about a clinical trial. And if they feel educated, empowered, and engaged enough to say, "Yes, I want to participate," they have the ability to be able to either consent right on site and go through the rest of the workflow.

(00:16:11):

They certainly can... We certainly offer sort of a hybrid solution where aspects of the workflow is digitized, and they can be done remotely, or depending on the trial mechanics, we certainly can offer some of the trial services at a patient's homes. And so for us, as we are listening and understanding the communities that we serve, we recognize that the solutions or the way we engage these communities is

not a one-size-fits-all, and it needs to make sure that it's customized to the communities that we serve. So we are certainly learning as we're implementing these trials. For us, it's very important as those that design these clinical trials are mindful that there's considerable amount of disparities, whether it's health literacy issues, technology broadband issues that we're facing.

(00:17:09):

Because, oftentimes, when trials have a lot of technology embedded into the design, not every community embraces technology in the same way. So for us, it's about making sure that the design parameters that are in the trials, that we've got to spend some time on how to make sure those communities that are not necessarily embracing some of the ways that we conduct clinical trials, that we can kind of bring it in a bite-sized fashion and we can get people who've historically not participated to participate.

Dr. David Fajgenbaum (00:17:42):

Yeah, I love that so much, as we heard about trust in the first set of comments, and it's around learning, right. It's learning from the communities that we're seeking to serve and also learning from the evidence that we're generating. I think that's so important. Thank you so much. So now let's turn to Jennifer Byrne, who's the founder, board chair, and CEO at Javara Research, where she facilitates community-level clinical trial access for both patients and also for providers. Ms. Byrne, your organization focuses on conducting pragmatic clinical trials at the point of care. Why is it important from both the patient and the healthcare system perspectives to drive clinical trials into primary care settings, and what are the benefits for patients that doing that?

Jennifer Byrne (00:18:22):

Yeah, thank you very much for joining this discussion. I think, first and foremost, this has been highlighted before, but I'm going to emphasize this again. I think it's really important to be building trust. Ultimately, in terms of integrating research and care, we are inviting patients together with healthcare systems to be part of the evidence-generating process. So I think no better way to build that trust and break down some of those barriers that have already been highlighted than to actually have a seat at the table and to be directly involved.

(00:19:04):

I think the second component to this to highlight would be that I'm going to say changing the narrative around clinical trials. I mean, oftentimes, in my experience, the perception, whether it's a patient perception or whether it's even a healthcare provider perception, is that the drug industry clinical trial process has been set up to serve pharma. And in fact, I think we have a more... a greater opportunity, again, to kind of change that narrative around how are we using clinical trials to address the unmet needs of the patients that we serve. Another way to describe that is really thinking about clinical research as an extension of the healthcare continuum.

(00:19:54):

And then I think the third important highlight to this in terms of why this is important from a patient and healthcare system standpoint is the opportunity by bringing this intersection together is that you're forming a natural partnership. You have an opportunity with healthcare consumers to be actually partnering with their local and trusted healthcare providers and healthcare systems. And again, I think it all leads back to that virtuous cycle of inclusivity and trust.

Dr. David Fajgenbaum (00:20:27):

Thank you so much, Jennifer, for going through that. I really liked your reframing around thinking about this less in terms of drug development, evidence generation in that context, but really evidence generation for the patient and being really patient-centric. Thank you. So now I'm pleased to introduce Ms. Brisbane. Would you tell us a little bit about your experiences participating in a clinical study as a patient? And we're really interested to hear what motivated you and your participation.

Wanda Brisbane (00:21:00):

Okay. My experience has been an awesome experience. I have never been in contact or been in that community where clinical trials were going on, but it's one word that has been used throughout this whole session, and that word is trust. And inside of the word trust, you've got us. So it takes us to go out into the community, let them know what's going on with clinical trials and what the outcomes will be. My experience was awesome. I had trust in my primary care physician, and when he approached me about it, I told him yes immediately. The workers themselves, the employees in that time, have been awesome in every way. They have made me feel comfortable.

(00:21:51):

They have made me feel secure, and I know that all of this will benefit someone else. And it's all about being made comfortable and feeling assured that what is happening or what's going on with you will also help someone else. I've been talking to some friends in regards to this, and they, just as I was, we had no idea these things were going on. So it takes getting the word out into the community, building that confidence and trust with the community. And thus, it will cause others to be interested in shaping the lives of others through clinical trials. So, for me, it's been an awesome experience, and I thank each and every one of you, but the main thing to me, everyone has the same concept, is trust. Thank you.

Dr. David Fajgenbaum (00:22:48):

[inaudible 00:22:48]... Thank you so much for sharing that. It's so great to hear about your positive experience. This is why all of us do what we do is to help patients, and to hear that you had a positive experience on the way... along the way is amazing. So, at this stage, I want to actually ask all of our panelists to turn your cameras on for these next round of questions.

(00:23:06):

We've heard initial perspectives from each of you about the role of post-market clinical studies. Now, let's address some of the challenges that you face. So I'm actually going to turn to Ms. Byrne first with the first question. What are some of the challenges you see most, and are any of those challenges shared by both patients and clinicians?

Jennifer Byrne (00:23:27):

Yeah, I mean, I think a couple of things. I think around trust. I mean, at the heart of establishing trust, I believe that you really have to start with education. So I think it is about educating, and it just cannot be, I think, overemphasized the importance of educating. And oftentimes, we talk about educating the patient, but I believe that we have plenty of opportunity and need to be educating the healthcare organizations. And Dr. Brown talked about all of the challenges that we have at a system level.

(00:24:06):

There are economic constraints, resource constraints, but I think that it really begins with kind of educating. And again, I'm going to really describe it as starting those conversations around what I described to be the expanded value proposition of research. And the expanded value proposition around what a high-touch clinical research experience can mean to a patient isn't just the data that

ultimately is collected for the evidence generation, but it really has to do with exceptional care and thinking of clinical research in a way as providing exceptional care delivery models.

(00:24:48):

And again, the upside to that comes towards, again, just more patient education around their own medical conditions, the importance of compliance, the importance of communication when something's not working or when something's working well. So I think it really... the challenge is just being mindful around how we better educate and articulate the expanded value proposition.

Dr. David Fajgenbaum (00:25:19):

Thanks so much, Jennifer. So we're running short on time, so I might actually suggest we do a rapid fire for challenges for our other panelists. So if our three other panelists, feel free to unmute and go in whatever order you see fit, but maybe just a rapid fire, just maybe 15, 20 seconds from each of you on what are some of the other challenges and let's hope that there's some recommendations in our next section of this session that are going to address some of those challenges. Ramita, Sam, Wanda.

Ramita Tandon (00:25:52):

I'll go. Listen, I think I addressed it a little earlier. I mean, the real world that we're facing is that as our consumers are coming into our stores and our pharmacies, they're asking the fundamental questions around what a clinical trial is. And so we have been very focused on, just again, that baseline understanding and educating and empowering our communities to feel comfortable to participate.

(00:26:19):

That's just the real world we're facing today, particularly in our communities in deep South and the rural parts of America, where research oftentimes haven't tapped into those communities. And so that's the day-to-day that we're confronted with. And so it is spending that time but also being mindful of a lot of the challenges our consumers are facing around health literacy, digital literacy, and just embracing technology overall as we create more sophisticated and complex clinical trial programs.

Dr. David Fajgenbaum (00:26:49):

Thanks so much. Sam or Wanda, any additional challenges that you'd add in?

Wanda Brisbane (00:26:54):

I totally agree. It would take education and getting to the grassroots. If you can get there and allow the trust and confidence to build with the community, it will make for a better environment for everyone that goes into them. And even just hearing about it, reading about it more. I haven't seen anything written. This is my first trial. I'm just going into my second trial. So if we can get more out to the community and invite them into the community, you'll get more participation and the confidence as well.

Dr. Samuel Brown (00:27:33):

I think from a health system at a brass tax level, I think we need this... the pragmatic evidence generation to be seamlessly clinical. We need to be able to have clinicians functioning as clinicians carrying out research procedures because I think if we try to employ the IND model, the docs and APCs and nurses are exhausted, so they have to be able to implement it in the course of their clinical work. And if we can get there, I think we've got a lot of exciting future ahead.

Dr. David Fajgenbaum (00:28:08):

Well, I just want to thank all of you so much for sharing your perspectives. As a physician and a patient myself, I can tell you that I am so thankful for all of you on this panel and also so thankful for the group that worked to put this report together through Reagan-Udall Foundation. I might close with just a quick analogy, and that's that Commissioner Califf often talks about drug development as being like soccer.

(00:28:34):

You need a lot of shots on goal, and every once in a while, it gets through the goal, but a lot of times, it has to go off of the goalie, or it's some random things have to happen. And I would say that what we're talking about with evidence generation is a little bit more like being in the red zone in football.

(00:28:49):

So you're inside the 20-yard line. You're close to the end zone, but the last 20 yards are often the hardest. The system gets really complicated. Even though we're really close to the end zone as we have an FDA-approved label, this last little bit can be really challenging. So thanks to everyone from the panel. As a board member for Reagan-Udall, thanks to all of you for your participation, and Susan, really I'm happy to turn it over to you for the next part of the panel.

Susan Winckler (00:29:15):

Fabulous. Well, thank you, Dr. Fajgenbaum, Dr. Brown and Ms. Byrne, Ms. Tandon and Ms. Brisbane. I think, Wanda, we'll be coming back to you to help with that part because that was just powerful, and it helps us get to the... across the... finish those last 20 yards. So thank you all so much.

(00:29:34):

I'm going to turn now to Dr. Richard Schilsky. Dr. Schilsky is chair of the foundation's board of directors, and he also chaired our expert panel that generated the report released today. He's going to share an overview of the project and facilitate remarks from a few members of our expert panel. Dr. Schilsky, if you are ready, I'm going to hand it over to you.

Enhancing Post-Market Evidence Generation for Medical Products

Moderator: Richard Schilsky, MD, Board Chair, Reagan-Udall Foundation for the FDA
Robert A. Harrington, MD, Weill Cornell Medicine
Adrian Hernandez, MD, MHS, Duke University School of Medicine
Russell Rothman, MD, MPP, Vanderbilt University Medical Center
Joanne Waldstreicher, MD, Independent Board Director and Consultant

Dr. Richard Schilsky (00:29:58):

Thank you so much, Susan, and good afternoon everyone. Thank you for joining our webinar today. As you've heard, earlier this year, the foundation initiated a project at the request of the FDA Commissioner to develop recommendations for improving post-market evidence generation for medical products. Specifically, we were asked to focus on prospective clinical studies that leveraged the US healthcare system and were, therefore, pragmatic in their design and operations.

(00:30:29):

Ideally, such studies would support regulatory submissions for new indications or other revisions to labeling. We were asked to consider actions that FDA, in particular, could take to enhance post-market evidence generation while recognizing that all stakeholders in the healthcare ecosystem have a role to play to expand and accelerate the evidence-generation process.

(00:30:52):

Now, as new medical products are entering the market more quickly than ever, often based on smaller clinical trial data sets, it's increasingly important to continue to learn about them throughout their lifecycle. Post-market studies provide an opportunity to expand indications, learn about safety and efficacy in more diverse patient populations, optimize drug dosing, and assess comparative effectiveness with other products. Such studies seek to answer clinically meaningful questions and resolve gaps in clinical evidence that directly impact how care is delivered in the US with the goal of improving treatment outcomes for all individuals.

(00:31:31):

The recommendations we'll summarize today if implemented with the support of the FDA, other federal agencies, health systems, payers, clinicians, and patients and their families, have the potential to simplify and accelerate post-market evidence generation and to begin to realize the vision of the learning healthcare system. So, on the next slide, I just want to acknowledge that these recommendations were developed by a panel of expert clinician investigators, some of whom you will hear from shortly. You see all of their credentials. They come from a variety of backgrounds, and you can read their bios in the full report.

(00:32:12):

Now, moving on to our methodology. Over the preceding nine months, we conducted a series of round tables with experts in various fields who provided insights into what changes and incentives are necessary for health systems, clinical researchers, clinicians, patients, payers, sponsors, and even IT providers to participate in post-market evidence generation studies. We also have listening sessions with frontline clinicians and patients to gauge their interest in research participation and the barriers to doing so. These meetings, along with the extensive experience of the expert panel members and review of pertinent FDA guidance documents, led to the recommendations we will now present.

(00:32:58):

In the time available, several of our expert panel members will briefly summarize the recommendations presented in detail in the formal report, and viewers are urged to review the full report for a complete discussion of the context and rationale for these recommendations. So let me begin with the two overarching recommendations in the report. Perhaps not surprisingly, first and foremost, many features of clinical studies need to be simplified to enable them to be embedded in routine clinical care. These include simplifying protocol objectives that endpoints broadening eligibility criteria and streamlining adverse event reporting and required data collection. Reducing the administrative requirements of studies is essential to encourage participation by clinical sites and frontline clinicians.

(00:33:52):

And the informed consent process must be greatly simplified to provide useful information to patients. Creating and implementing standard structured clinical data elements and automating electronic data capture is necessary if post-market clinical studies are to be successful and resource-efficient. You'll hear more about these recommendations in detail from my colleagues in this session. Second, we recommend that an interagency task force should be established led by FDA and comprised of FDA, NIH, CMS, the Office of the National Coordinator, and sponsors to establish guiding principles and minimum requirements for post-market evidence generation studies that allow each agency to achieve its mandate while simplifying the entire evidence generation process.

(00:34:47):

Doing so, we believe, will help transform our currently fragmented evidence-generation process to a more systematic approach where incentives and systems are aligned to enable continuous learning during care delivery, the benefit of current and future patients. So now it's my pleasure to introduce Dr. Robert Harrington. Dr. Harrington, formerly Chair of the Department of Medicine at Stanford, is the recently appointed Dean of Weill Cornell Medicine and Provost of Medical Affairs at Cornell University, and Bob will review the next set of recommendations in our report. Dr. Harrington.

Dr. Robert Harrington (00:35:25):

Thank you so much, Rich. It's really a pleasure to be here, and a lot of what I'm going to talk about has been made reference to by the panel that preceded this report out. My job is really to cover the recommendations that deal with implementation of pragmatic evidence-generation studies. These will be listed in the report as recommendations five to 10, and they're very related to one another, and I'll try to talk about them in groups. First off, as Rich has already noted, not all post-market research studies will be appropriate or amenable to the pragmatic study design, but some are, and in those situations is really what we're talking about.

(00:36:08):

How do we generate pragmatic evidence that would allow us to make the case that evidence generation can be more efficiently and effectively integrated into routine care? And that really is what these recommendations are getting at. How do we better integrate evidence generation into routine care? I thought Dr. Brown, in the last section, said it quite well. He said, "We need to have clinicians be clinicians and that the evidence generation is going on as part of routine clinical care." So the first is that we recommend that there be the establishment of a value proposition for healthcare leaders to incorporate post-market evidence generation studies into routine clinical care.

(00:36:54):

This is going to require that we think about things like evidence generation as a quality metric, something that healthcare leaders can be held accountable for. We've heard over and over during our group interviews in the work that we had done, as described by Rich in the prior slide, that financial incentives for individual clinicians are not the only issue that needs to be attended to, and in fact, in many cases, financial incentives are insufficient. What we really need to do is to think about what's important to clinicians. And part of what's important to clinicians is that the evidence generation not interfere with their routine work.

(00:37:37):

That gets us into the second recommendation here to emphasize the importance of stakeholder engagement. Stakeholders include frontline clinicians, it includes clinical operations staff, it includes patients or participants, it includes families and caregivers, and we've heard a variety of things, but let me stress a couple. Number one, relevant questions. These need to be questions that clinicians, patients, and their caregivers care about. Number two, define the standard of care so that things can be compared against that standard of care or on top of that standard of care.

(00:38:19):

We really don't want to interfere with what is the standard of care in these types of studies. And number three, streamline. Streamline study operations. These are not IND types of investigation that needs to be done. We need to streamline all things surrounding the process of evidence generation. The next couple really get at that. Simplify study-related documentation and requirements. In the typical IND study of evaluation of a new drug, there are an enormous number of forms and documents and requirements that sites need to adhere to. That's not what we're talking about here. We need to make

this as simple as possible. No pretest surveys, limit the amount of questionnaires, limit the amount of documentation that we're asking for.

(00:39:14):

Credentialing is always a difficult part of the research process. In an evidence generation in a pragmatic way, we need to have a streamlined, systematic approach to credentialing investigators. What this might include is a nationwide database not held by one individual sponsor, not held by one individual contract research organization, but a centralized system, perhaps done under the auspices of this interagency working group that we've called for that can hold onto site and credentials that lists who has appropriate credentials to be an investigator.

(00:39:57):

And in these where we're citing that, what we're really looking for is clinicians working at the front line. Finally, in a similar way to a centralized data bank, master service agreements between sponsors and the sites that really focus in on pragmatic evidence generation. These are not master service agreements dealing with typical research questions. These would be master service agreements that deal with the question of how do we get work done related to pragmatic evidence generation? With that, Rich, I'll turn it back to you for the next section.

Dr. Richard Schilsky (00:40:38):

Okay, thank you very much, Bob. It's now my pleasure to introduce Dr. Joanne Waldstreicher. Until recently, Dr. Waldstreicher served as chief medical officer at Johnson & Johnson. And so Joanne is going to cover recommendations... the next set of recommendations in the report. And Joanne, please take it away.

Dr. Joanne Waldstreicher (00:41:02):

Thank you so much, Rich. I'm really going to focus on data collection and algorithms which are recommendations 11 to 17 in the report, and following along from the themes that you've already heard, simply focus only on the information that's necessary to answer the research questions with a limited number of objectives and endpoints. And the critical part is utilizing standardized data as best as possible that's readily available in the electronic health record and claims data and does not always need to be manually entered into a separate parallel system and does not need to be adjudicated or validated during review of the study data at the end.

(00:41:43):

And so the first recommendation is that, whenever possible, required data elements should be available as structured data elements in the EHR or claims data. Also, the required data elements should be aligned as best as possible with clinical standards of care and collect data elements at time points consistent with clinical care guidelines and workflows rather than a separate schedule for the research study. The next one is inclusion and exclusion criteria and study endpoints, which, again, should be written in a standardized computable phenotype format whenever possible. And this will also help facilitate automatic matching of patient characteristics to clinical study requirements for enrollment.

(00:42:27):

The next recommendation is really on EHR systems, which should be modifiable, if needed, and where possible, to capture key health outcomes in a structured format. The clinical research community should work collaboratively with EHR vendors to create minimum common data elements for common diseases that capture important clinical descriptors and outcomes in a structured format. Now, I want to focus on endpoints. Data collection using EHR and claims data that does not require separate data entry and

additional adjudication or a validation is important for implementation of an integrated, straightforward, and resource-effective pragmatic evidence-generation study.

(00:43:15):

We recommend that the FDA should consider issuing guidance on development validation and use of algorithms to identify endpoints derived from EHR and or claims data. Once these endpoints are validated for a specific purpose, these validated endpoints should be accepted for new studies in similar patient populations without additional validation efforts. Next, we recommend that the FDA, in collaboration with sponsors and other organizations, should maintain a library of commonly used and accepted algorithms for post-market pragmatic evidence generation for everyone to be able to see and use and learn and use in their research studies.

(00:43:59):

Algorithms intended to be used in post-market pragmatic evidence generation studies should be pre-specified in the study protocol and, of course, discussed with the FDA prior to study launch. Guidelines for identifying and using valid algorithms are really important for post-market pragmatic evidence generation used in regulatory decision-making. Using the FDA Sentinel System as a model or ODYSSEY or PCORnet, a library of commonly used and accepted algorithms for post-market. Pragmatic evidence generation could serve as a resource for future studies and also facilitate a learning healthcare system.

(00:44:41):

Now we understand that insurer, billing, and coding instructions can change over time, which may affect documentation in the EHR and coding trends and claims data. Therefore, algorithms will need regular review to ensure that the code lists used to populate them are updated. Focus should be on developing a systematic process for validating EHR and claims endpoints that can be widely leveraged for future studies and utilizing algorithmic adjudication in place of manual where appropriate. Finally, I want to focus on adverse events and other study documentation. Sponsors and the FDA should minimize the time and cost burden to the healthcare providers and the healthcare system for a separate entered data, separate documentation of study-related procedures, concomitant medications, and reporting of adverse events.

(00:45:36):

Adverse event reporting, as an example, is labor-intensive, and requirements for adverse event reporting for pre-approval like phase two... phase one, two, or three studies may not be necessary for post-market pragmatic evidence generation studies of medical products with known safety profiles. For post-market studies of products with a known profile, real-time adverse event reporting we believe should be limited to unexpected high-grade treatment-related serious AEs as much as possible. So our recommendation is to perform the analysis of adverse events at the end of the study using the EHR and or claims data for event analysis rather than requiring real-time reporting documentation of most AEs to the FDA by the frontline clinician and staff within a specific time window during the study.

(00:46:34):

Again, unexpected treatment-related serious AEs should continue to be reported expeditiously by the study investigators to the FDA. There is an FDA guidance for industry determining the extent of safety data collection needed in late-stage pre-market and post-approval clinical studies and the ICH guideline E19 on the selective approach to safety data collection in specific late-stage pre-approval or post-approval studies, which supports selective collection of AE data. Although this guidance is available on targeted safety data collection, it has not been as widely adopted or used as it could be.

(00:47:17):

And in a setting of a pragmatic trial where there's access to the EHR and claims data, important medical events or adverse events are already being passively collected in the EHR and claims data by study clinicians taking care of patients and could be analyzed at the end of the study without the clinical team needing to do separate data entry or real-time reporting of most of the adverse events during the study unless they are serious, drug-related, and unexpected. And we believe this will significantly unburden the clinical sites and clinicians and let clinicians be clinicians.

Dr. Richard Schilsky (00:47:58):

Thank you so much, Dr. Waldstreicher. To review the next set of recommendations, it's my pleasure to introduce Dr. Adrian Hernandez. Dr. Hernandez, as many of you know, is Executive Director of the Duke Clinical Research Institute and Vice Dean for Clinical Research at Duke University School of Medicine. Adrian.

Dr. Adrian Hernandez (00:48:17):

Okay, thanks for having me here. So I'll go through the overall recommendations that are number 18 through 21 and summarize these. But briefly just want to say through this process, one of the things that we observed is that the FDA is open to pragmatic studies. There are examples for which the FDA has encouraged and acted on evidence that is generated through pragmatic studies. However, it was clear through our process that sponsors and investigators would benefit more from clear and definitive guidance regarding acceptable documentation and evidence generated from pragmatic trials, point of... that use point-of-care processes or decentralization of clinical trials.

(00:48:58):

And especially important with comparative effectiveness studies were electronic health record data or claims data is also being used. And to align with that interest in simplifying trials and using data that's already being generated as part of routine life or routine healthcare, there's a number of things that would be a benefit for the community regarding understanding with clarity what study processes and data collection can and should be used.

(00:49:29):

And so, more specifically, that the FDA could provide further guidance as it's been doing regarding the scope and scale, and quality of evidence that they would consider from post-market pragmatic evidence generation studies to help provide some understanding regarding how this can be helpful to expand indications, modify labeling and close evidence gaps for our use of a marketed medical product, and also making sure that that's a distinctive from some of the guidance that they may have for preapproval of clinical trials for new medical products.

(00:50:05):

Another recommendation has to do with really helping others understand what's possible. And so helping close the guidance to dissemination implementation gap by promulgating what are the principles and processes within the FDA so that others can learn from other studies that have been performed in this manner. And so, in this way, that there can be better translation of intention or guidances across agency and across different communities that can develop and act on these pragmatic studies.

(00:50:46):

Also, it would be very helpful to have some type of approach where there can be a consultative body within the agency to help make sure that these processes that are being used for streamlining trials and also data collection can be also implemented across different clinical areas and also be done so in a

consistent way. And then also learn from new cases as they come up when there's a pragmatic study that generates a necessary evidence to make a decision.

(00:51:21):

There's also a great possibility to help everyone learn within the FDA and outside by devising a series of use cases and specifically focusing on how to really focus on parsimonious study collection to really understand the benefits to risk that is needed for a post-market study that's different than say a new drug, a new approval study, and how this could be acceptable to FDA for regulatory purposes and also understand the other contexts that may be important.

(00:51:55):

And then, finally, also it's important to consider demonstrating this through innovative projects, pilot demonstration projects in partnering with agencies such as NIH, PCOR, and CMS and industry so everyone can learn together on how to design and implement these studies that can be regulatory, enabling and partnering across ecosystem with health systems, payers and others. So with that, Rich, I'll turn it back over to you.

Dr. Richard Schilsky (00:52:22):

Great, thanks so much, Adrian. So, next, let me turn it to Dr. Russell Rothman, who is Senior Vice President for Population and Public Health at Vanderbilt University of Medical Center and Director of the Institute for Medicine and Public Health at Vanderbilt. Dr. Rothman.

Dr. Russell Rothman (00:52:42):

Thank you, and good afternoon everyone. You heard in the first session of today's meeting and from Bob Harrington about how critical it is to engage patients, clinicians, health systems, and the larger community for evidence generation and research. And many of the recommendations from this report reinforce this critical component of research and address some of the barriers mentioned in the earlier session. The ultimate goal of research is to improve the health of people and their families and their communities. So it is paramount that post-market evidence generation be centered around patients and other key stakeholders that will ultimately be impacted.

(00:53:29):

Patients, clinicians, and other key stakeholders should therefore be engaged in all aspects of this research, including study, design, implementation, evaluation, and ultimately dissemination. The performance of pragmatic studies embedded into the real-world helps to more fully embrace stakeholders and to understand how medical products may perform in the real world setting. We need to design studies that meet patients and families where they live and work and not just to expect them to come to a sterile research environment. This is particularly important for reaching more diverse populations in research. The committee has several recommendations to enhance the involvement and experience of patients and other key stakeholders.

(00:54:18):

The first three bullets on this slide refer to removing barriers to participant engagement. This includes reducing barriers to participation, including the cost for patients to participate, such as transportation costs, parking costs, potential copays, time off work. But also, we need to consider designing and supporting studies that take place outside of the traditional health system locations. And some of these were mentioned earlier, but these might include studies that take place in community pharmacies, community health centers, community centers, or even studies that engage participants in their homes or at work, often using mobile devices and centers for data collection and monitoring.

(00:55:08):

But as was also mentioned earlier today, we also need to consider other potential barriers and issues such as health literacy and digital literacy, limited English proficiency, cultural issues, trust issues when we are designing studies and address these issues in order to optimize engagement. It is important that we design these studies with input from target participants and the community to ensure we can reach these diverse populations that represent the communities we serve. For studies that require products to be delivered in the healthcare system, we also need to engage clinicians, nurses, health system leaders, and other staff, as was mentioned earlier today.

(00:55:57):

We need to engage these systems in order to understand the barriers and opportunities to implement new evidence in the healthcare system setting. New evidence is not helpful if it is not implemented. In addition, we need to examine ways to improve the consent process for both the research team and the study participants. While we recognize that there are a lot of regulatory requirements related to consent, the current consent process is too complex, long, and burdensome with a lot of jargon and regulatory and legal components. The ultimate goal of consent is to inform and get appropriate engagement and approval from our study participants.

(00:56:43):

However, there remains a lot of heterogeneity in how different organizations interpret the requirements for consent and add additional local, legal, and other language. We need to remember that consent is a process that is ultimately about good health communication between the study team and the participants. We need to support innovative approaches to improving the consent process, including processes that embrace electronic consent processes, use of infographics or other video and visual tools to explain studies and confirm comprehension, a focus on the key components of the study with the ability for participants to dig deeper into the legal aspects as desired. Thank you.

Dr. Richard Schilsky (00:57:34):

Great. Thank you so much, Russell. So to wrap up this section of the meeting, just want to talk a little bit about how these sorts of post-market evidence-generation studies are funded. And this has come up already, even in the first panel, where we recognize that garnering financial support for these types of studies can be challenging because the return on investment may be less immediate or tangible. The goals of the study may be to improve public health or treatment outcomes more so than to advance a product to regulatory approval and into the marketplace.

(00:58:14):

So the new evidence-generation paradigm that we've presented today really requires different assumptions about how priorities are established, how different segments of the healthcare ecosystem will be expected to provide support, and how providers will be incentivized to participate. The paradigm is grounded in the expectation that all components of the healthcare ecosystem have an obligation to generate new knowledge that improves clinical care or public health and will benefit the whole system by doing so.

(00:58:47):

And I'll just say that, as we went through the various roundtable discussions, everybody is supportive. All segments of this community are supportive of generating new knowledge, but where there's not unanimous support is whose responsibility it is. The payers say, "Our job is to pay for things that are proven beneficial." The health system executives say, "Our job is to implement the knowledge that's

created by others." The research community says, "Of course, our job is to do cutting-edge research, not necessarily to spend time on closing clinical evidence gaps."

(00:59:31):

But the fact of the matter is that if we're going to create a systematic approach to learning in this country, all of these groups and more have to commit to the idea of generating new knowledge every day in the course of clinical care because everybody ultimately benefits from doing so. Thus, our final two recommendations are that sponsors, payers, federal agencies, healthcare systems all should be expected to contribute significantly to support such studies, whether through financial support, through resource support, through personnel support, through technology support, everybody has something that they can contribute to advance studies that are done in the post-market setting.

(01:00:23):

Nevertheless, we've recognized that funding post-market evidence generation studies is challenging and will need to extend beyond typical sponsors. In fact, we feel the federal government may need to step up to establish a precedent for how such studies are supported, perhaps through increased use of public-private partnerships. And there are many such examples already going on that are highlighted in the report. So now I would like to invite all of the panel members who have presented their recommendations to turn on their cameras. I think we may have time for just a few questions, and we're happy to take those. I know, Susan, I think you've been monitoring the chat for questions, so please feel free to send anything our way.

Susan Winckler (01:01:11):

I have been, and it's really helpful to have just really appreciate the engagement and the questions that are coming in. One had to do with the role of patient-generated health records. And so I wondered if any of the members of the expert panel would want to speak to that. And is this an opportunity to perhaps drive that, you know, that we would have some synergy in the patient-generated health record and their use in research?

Dr. Richard Schilsky (01:01:42):

I wonder if, Russell, you might want to pick that one up.

Dr. Russell Rothman (01:01:48):

Yes. I mean, I think there's certainly opportunities there, and we definitely want to explore more ways to get patients more engaged at all levels, and patients sharing their own health information is certainly one of those avenues. I think it could generate a lot of novel information that investigators may not have originally thought to collect. I think we would need to really think about how to do that in a way that allows for validity of the data and ability for analysis. But I think it is definitely an important area for growth.

Dr. Richard Schilsky (01:02:29):

[inaudible 01:02:31]-

Susan Winckler (01:02:31):

[inaudible 01:02:31] it strikes me as interesting... And sorry, go ahead, Rich.

Dr. Richard Schilsky (01:02:36):

No, I was just going to say it's a very interesting idea because the only participant in the healthcare system who knows everything about their healthcare is the patient. Different doctors know about their part of the care delivery system, they know about their specialty, they know about their intervention, and all these different components of the system are documenting in various ways, many of which don't talk to each other in various systems that don't communicate well, what's happening to the patient.

(01:03:12):

So to find out what's going on in a holistic fashion with any individual patient is very challenging. But the one individual who does know about it is the patient. And so, finding ways to inform patients to improve their health literacy so they can report accurately to collect their information in a more standardized and centralized fashion and be sure that it provides valid information that's useful for decision-making is, I think, a wonderful aspiration that the system that we envision, could aim toward.

Susan Winckler (01:03:53):

Excellent. There's another question, and this is about querying. If there are specific examples of situations where the FDA accepted prospective pragmatic studies for regulatory requirements. Now, nobody on screen or in the panel is at FDA, so I know that we can't speak to the whole experience there. So I guess I'll rephrase that to say, are any of our expert panelists who are here today, can you think of examples where FDA accepted prospective pragmatic studies for regulatory requirement?

Dr. Joanne Waldstreicher (01:04:33):

Susan, I'm not sure that there has been a study that it has been... that has encompassed all of the things that we've talked about today. But however, in the past, there have been some cardiovascular studies and some statin studies, in particular, like the heart protection studies, which was set up as a very large but very simple study with, I think, one or two-page case report form, if I remember correctly. So there are examples, and it did lead to a label change. I should also add that a more recent example is the RECOVERY trial that was done in the UK. And although I'm not sure that it was submitted to the FDA, the data were obviously of critical importance for public health and widely adopted.

Dr. Adrian Hernandez (01:05:23):

A couple other examples here to add to Joanne, and I think what Joanne talks about here is that the recommendations are really talking about holistic from end to end in terms of how we can have easier, simpler trials, and pragmatic trials here. There are definitely examples with that that one calls a pragmatic trial, but we're talking about this in the spectrum pragmatism.

(01:05:48):

A recent example of that is a trial called EMPA-KIDNEY that had a lot of pragmatic features in terms of its implementation, also developed by the Oxford Group in collaboration with a sponsor. And then there are also several examples of going back in the olden days, so to speak, of gusto and thrombolytics. That's kind what we're trying to talk about is how we get to something simpler that was very important, actionable, very parsimonious data collection that helped understand the benefits to risk for our major medical product.

Dr. Robert Harrington (01:06:27):

Yeah, just building Susan a little bit on both Adrian, Joanne's point, I think some of the cardiovascular trials, particularly the very large trials, there has been a willingness to accept stripped-down data

collection, more facilitated... more streamlined monitoring, things like no need for SAE reporting when SAEs relate to study endpoints.

(01:06:51):

So there have been pieces of it, but I think Adrian's spot on that we're try to do in this report is really do the holistic approach end to end. FDA has certainly been amenable, at least in the cardiovascular division, at taking pieces of pragmatism. Now the question is, can we use the whole package?

Susan Winckler (01:07:11):

You might have the line there, Dr. Harrington, with the pieces of pragmatism to getting to the package of pragmatism, although we'll all have to practice saying that.

Dr. Richard Schilsky (01:07:21):

Maybe I can jump in with just one more example. So I'm the oncologist in the group, and so I can't omit an example from oncology that's currently ongoing. And it's highlighted in the report, among others, and it's called the Lung Pragmatic Study. So this is a study that is really conducted as a public-private partnership between FDA, NCI, two drug companies, Merck and Lilly and Friends with Cancer Research, with some participation as well from the foundation for the NIH. And all of these groups came together to address a very simple question.

(01:08:01):

There was preliminary data from a previously published study that using two drugs in combination, ramucirumab, and pembrolizumab, produced better survival of patients with advanced non-small cell lung cancer than using just ramucirumab alone, which was the standard of care. The FDA was very interested in validating that preliminary signal of improved survival. Basically work with all of the participants in this public-private partnership to say, "Bring us a definitive, simple, prospective randomized clinical trial. We're only interested in one endpoint overall survival. We're not interested in tumor response. We're not interested in tumor progression.

(01:08:49):

You don't have to do any scans. You don't have to measure any lesions. All we want to know is the preliminary signal of two drugs producing better survival than one validated. Similarly, since both drugs are already marketed in the same patient population, you don't need any complicated adverse event reported. Just document any serious unexpected adverse events, and that's all that we're looking for."

(01:09:14):

So this is an ongoing trial. It's accruing very rapidly in hundreds of sites around the country. We hope and expect that FDA will certainly accept the data. Whether or not it'll validate the preliminary findings remains to be seen, of course. But I think it's a wonderful model for how practical simple trial designs can be used to address clinically meaningful endpoints like does two drugs improve the survival of patients with lung cancer compared to just one.

Susan Winckler (01:09:48):

So that's one that will be... we and many will be watching to see how that progresses and then how it's considered. We did also have a note submitted by one of the webinar attendees that INVEGA SUSTENNA PRIDE pragmatic trial added to their label with real-world data component as an endpoint. So just a flag there.

(01:10:15):

And then I'll note we did also have a commentary about personal health records being broader than patient-generated records. And so, there may be even more of an opportunity there to generate a research-ready database. So I think I would say, Rich and panelists, we've gone through the questions that we had here and probably have a minute or two if you wanted to provide final thoughts before we turn it over to Commissioner Califf.

Dr. Richard Schilsky (01:10:47):

Well, I think, just to wrap up, we hope that the FDA and the broader research community will find this report valuable. The key is not to just sit back and read the report. The key is to try to implement the recommendations in the report in everything that we do in clinical research every day. I'm a firm believer that much of the complexity of clinical research is of our own making. We are the ones who've created excessively complicated eligibility criteria. We are the ones who demand more and more data collection. Some of this is driven by just the intense curiosity of the research community. Some of it is driven by fear of failure and going before the FDA and not having an adequate dataset.

(01:11:37):

But we can also be the ones who help solve the problem working with the agency and other interested parties to get to the core issue of what are the questions that need to be answered, what's the simplest way to answer them, and let's do it quickly and efficiently and generate reliable data that's applicable to as broad a population as is medically appropriate. And that's the way we're going to advance the improvement in health for our entire population. I want to take this opportunity to thank the expert panel members who were able to participate today. Two of our members, Dr. Judith Currier... Or actually three of our members, Dr. Judith Currier, Dr. Emily Largent, and Dr. Rick Gilfillan, were not able to join us today but certainly contributed equally to the development of this report.

(01:12:31):

I want to thank the panel members who's really spent in the last nine months devoting a lot of time and effort. You can see these are very busy people in their day jobs, but they took this very seriously. And in particular, I want to thank the Reagan-Udall Foundation staff, who helped keep us organized and on schedule and contributed a lot to the generation of the report that we are making public today. So thank you all. And at this point, if Commissioner Califf is on the line, we'll ask him to turn on his camera. And Commissioner, we hope you've had a chance to take a look at this report. More importantly, we hope it's going to be helpful to you and your colleagues at the FDA, so we'd love to hear your reaction.

Commissioner Remarks

Robert M. Califf, MD, Commissioner of Food and Drugs, FDA

Commissioner Robert M. Califf (01:13:22):

Thanks, Rich, and first of all, I want to express my deep appreciation for the work that you guys have done at the Reagan-Udall Foundation. It's been quite a year for you all. You produced a great report on the Human Foods Program, the Center for Tobacco Products, and a recent one on improving understanding of FDA and FDA-related products, AKA dealing with misinformation. That's given us really excellent advice and guidance for improving our work at the FDA. This report we're discussing today is every bit as important.

(01:13:58):

So again, I just want to say the Reagan-Udall Foundation is providing tremendous support for the mission of the FDA. A little bit of history here. Prior to the enactment of the Kefauver-Harris

Amendment to the Food and Drug and Cosmetic Act in 1962, clinical trials were developing as a tool to advance medical knowledge. But they were not seen as essential to the development of medical products. I know that sounds odd, but the evidence you needed was a doctor who said this product is good.

(01:14:30):

The evidence generation system was transformed with the Kefauver-Harris Amendment because of the thalidomide disaster. And it specifically says what's required to have a product put on the market is evidence consisting of adequate and well-controlled investigations, including clinical studies conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by, such experts that the drug will have the effect it reports or is represented to have under the conditions of use, prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(01:15:17):

Now, that's a mouthful, but you'll notice that it's very prescriptive. This is a law of the land and really forms of basis for our pre-market evaluation system for medical products. Device regulation's a bit different, but same basic principles and this remarkable change in the law stimulated what I think was a revolution in clinical trial methods and quality due in no small part to the hard work of the FDA. While the system of pre-market clinical trials has plenty of room for improvement, it's fundamentally working well, in my view, and successfully separates medical products with benefits that exceed risk for specific indications from medical products that have risks that outweigh the benefits.

(01:16:05):

I want to be clear that from my perspective, we'll continue to work on improving the pre-market trial system, especially in areas where precision medicine is moving quickly, such as cancer and rare diseases, and through the FDA's accelerated approval pathways. But this report covers a different domain than we need to define and improve now, and I believe the time is right. The pre-market evaluation of drugs, biologics, and devices does its job, but it leaves many questions on the table after initial approval as these medical products move in the clinical use. How does a new treatment compare with other treatment options? Can treatments be combined, and if so, how? How long should the treatment be used? Is there a better dose? What's the value of the treatment?

(01:16:56):

Are the characteristics of patients that identify those with excess risk or special benefit? What about additional indications? The point of this report is that, in my view, is that although the fundamental principles of clinical trials pertain to all trials, the best practices for implementation in the post-marketing phase are different. Unfortunately, the clinical trials enterprise has not previously done a great job in differentiating these different purposes for trials in a manner that enables a robust fit-for-purpose post-marketing evidence generation system. These post-market questions stretch beyond the direct purview of the FDA and take us into territory that intersects multiple federal agencies, provide our organizations, clinicians, and payers and patients have much at stake in getting this right.

(01:17:54):

The net result of the fragmentation that you have referred to in this report and the fragmentation of responsibility in this phase is that we have no national system to generate the evidence we need to optimize the screening, diagnosis, and treatment among the multitude of medical products on the market. Yet we continue to spend over $4.3 trillion for health outcomes that are inferior to other high-income countries, exemplified by our significantly shorter life expectancy compared with peers. While this post-market phase of medical products is not FDA's primary responsibility, we do have clear

responsibility for safety in the post-market phase and evidence to support new indications for medical products.

(01:18:45):

Our mission statement specifically states, "FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate science-based information they need to use medical products and foods to maintain and improve their health." Study after study shows that less than 20% of major recommendations in specialty society clinical practice guidelines are supported by high-quality evidence. We cannot provide accurate science-based information when the evidence doesn't exist. Additionally, the recommendations in this report, if implemented effectively, could open up evidence generation for nutrition, dietary supplements, and health services interventions.

(01:19:37):

The report is a compilation of practical tactics that have been promoted in previous reports. There's nothing new here. But as you've stated, the comprehensive nature of the 30 recommendations gives us an excellent list from which to reform the system. I'll offer a few brief and general comments on them. The first two overarching recommendations call for a concerted direct approach to improving the degree to which post-market trials are efficient and affordable by reducing unnecessary complexity. How often have we all heard that, "We would love to answer this question, but we can't afford to do it." Above all else, we need to work together to make the conduct of trials less burdensome for participants and clinicians.

(01:20:24):

We hear a lot about being less burdensome for companies but not a lot about less burdensome for participants and clinicians. It's time to change that in this phase of research. By applying principles of quality by design, we should be able to enable many more trials to answer critical questions. While the mechanism will need to be worked out, we definitely do plan to work across the different agencies of the Department of Health and Human Services on these issues. The recent confirmation of Dr. Monica Bertagnolli as NIH director will certainly help support this collaboration. In fact, I had a chance to make my first join of appearance with Dr. Bertagnolli today at Friends of Cancer Research.

(01:21:07):

I think you're going to see some really interesting collaboration, not only between FDA and NIH but across HHS. Now, with CMS much more interested because of the Inflation Reduction Act. We take to heart the plea to create a more favorable regulatory environment for simplified, less labor-intensive post-market trials. As simple as it might seem, developing a lexicon that can be used by all concern to describe different types of clinical research is a fundamental issue that we intend to implement. Just use... A joint FDA-NIH committee is already working on this problem, and we plan to bring in the broader community during the course of the upcoming year.

(01:21:49):

Simply put, quality by design requires that we develop approaches that are generalizable for different purposes. A phase one trial of a new product demands different criteria for quality than a trial comparing products that have already been marketed with clear profiles. As long as the same terms, like pragmatic clinical trial or real-world evidence, have different meanings among different experts, we'll continue to see fragmented and slow progress. The implementation recommendations include a checklist of approaches that would improve site efficiency, reduce the burden on clinicians participating in research, and reduce the immensely frustrating issue of variability and contracting practices among institutions.

(01:22:35):

Investigators would likely welcome a central mechanism for credentialing that will reduce the mind-numbing redundancy of duplicating paperwork for each trial sponsor or NIH Institute. Multiple previous efforts have failed to bring contracting into a rational, systematic approach, but perhaps I think I've personally been on five different commissions working on that. But perhaps the momentum of multiple government and private elements working together, this vaccine variation can be dramatically reduced or eliminated. The remarkable progress in digitization of routine work should enable significant simplification of study, processes, and data collection. The ubiquity of electronic health records, claims data and wearable sensors should enable collection of more complex, more relevant data without the current massive human labor with its huge cost.

(01:23:30):

This is a place where artificial intelligence and machine learning should lead to the development of much more ability to clean up data and develop computable phenotypes to describe clinical status and endpoints. Across HHS, including the Office of the National Coordinator for Health Information Technology, NIH, FDA, and other agencies, we need to organize the library function, which you all have referred to nicely in several different dimensions, to make sure these advances accrue for public good. The recommendations for improving patient or participant recruitment enrollment are sensible. The issue of consent continues to be frustrating as there is general agreement that people would prefer simpler, less complex consent documents.

(01:24:15):

And like many aspects in our society, a digital approach offers a more interactive capability that can be adapted to the individual. However, progress has been limited. I urge more attention to the option of posting consent forms on clinicaltrials.gov in 2016. We made sure there's a place for that, and I believe that sunshine and research on these documents would likely stimulate needed to reform. The recommendation on payment... The recommendations on payment fall outside the primary remit of the FDA. I heard Dr. Brown refer to the thin margins of health systems. The margin of the FDA is zero, just to be clear about it. However, as we advocate and contribute what we can to the effort, there is wisdom in the concept that everyone can pitch in, and there's a compelling societal rationale for answering critical questions that currently go unanswered.

(01:25:12):

While the medical products industry should do its part, there's also wisdom in uncoupling the current product sponsor approach. Since medical products companies have direct financial disincentives from addressing questions that may reduce their revenue or profit, I would argue that health systems should have a positive incentive to learn so that they can focus on the strategies that matter. In summary, while we'll continue to improve our pre-market clinical trial system for medical products, mostly involving the FDA, the medical products industry, and a specific type of research enterprise, which is heavily focused on this type of trial, now is the time to make major renovations to our post-market system.

(01:26:01):

Technology is no longer our limitation. All of us would benefit from more knowledge of which medical products should be used for which patients and populations at a given point in their clinical journey. Just out of interest, I looked at my own immediate family, and there were at least 10 questions that are in front of us right now that no one knows the answer to, that our clinicians are making their best judgment about. Without evidence, it could be easily generated if we had such a system. So I appreciate the report. We're going to do our best, but we need everyone to pitch in to make this successful.

Closing Remarks & Adjournment

Susan C. Winckler, RPh, Esq., Chief Executive Officer, Reagan-Udall Foundation for the FDA
Robert M. Califf, MD, Commissioner of Food and Drugs, FDA

Susan Winckler (01:26:41):

Commissioner, thank you for reviewing and reflecting on the report and challenging so many in the ecosystem to do better. We can do better for you for those 10 questions in your family and for each of our families as well. So thank you so much. Thanks to everyone who joined us for the session today, and you can see the report at reaganudall.org. Commissioner, we are looking forward to the next projects that we will pursue for you.

Commissioner Robert M. Califf (01:27:11):

I think we've kept you busy. We intend to keep doing that. Thanks a bunch.

Susan Winckler (01:27:15):

Sounds great. Take care all.