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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

+ + +

STRENGTHENING THE NATIONAL MEDICAL DEVICE POSTMARKET  
SURVEILLANCE SYSTEM

+ + +

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9:00 a.m.

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Greenbelt, MD 20770

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M E E T I N G

(9:15 a.m.)

MS. RAYNER: Good morning. I'm so glad to see you all here.

I'm Anita Rayner. I'm the Acting Deputy Director for Policy and Administration in FDA's Center for Devices and Radiological Health, within the Office of Surveillance and Biometrics.

On behalf of CDRH, I'd like to welcome you to today's meeting about strengthening our nation's medical device postmarket surveillance system.

We're glad to see a number of you here in the audience. We also have a large number of people, actually a larger number of people, who are participating by webcast, and so we'll be trying to manage all of those details as we go through. For those of you who are watching by webcast, we intend this to be an interactive session, and we've set up an e-mail address for you to submit your comments or questions. We won't take those right away, but I wanted to give you that address right now, before I forgot. It will also appear on your screen. The e-mail you should send your comments and questions to is [cdrhpublicmeetings@fda.hhs.gov](mailto:cdrhpublicmeetings@fda.hhs.gov).

So as I mentioned, although our topic is far-reaching and pretty ambitious, our goal today is simple. We want to begin a national dialogue about where we should go in the future with respect to device postmarket surveillance. We want to talk about how to improve the way the Agency

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collects, analyzes, and acts on postmarket performance information for devices. That means that it's critical that we hear from all interested parties about whether the actions we're proposing are the right ones, whether we've forgotten something, whether we've overemphasized or underemphasized certain things, and we're basically here to listen and learn. So that's the overarching point of today.

And as most of you know, today also kicks off a series of three separate meetings running the four first days of this week, where today we're going to talk about the postmarket strategy, tomorrow we're going to talk about MDEpiNet, and Wednesday and Thursday we're going to be talking about registries. So I hope you will join us for all three of these sessions.

Let me run through the agenda really quickly. The first part of today, we've got an overview of the proposed strategy, and we're going to also ask our CDRH participants, who are sitting up here, to delve a little bit deeper into the strategy. But I'm also going to really, really ask for your participation and really sort of provoke you to ask us hard questions, as well as I'm probably going to ask you questions because we have established panels later on, but we don't always hear from everyone who wants to input their ideas.

After that we will have an Open Public Forum. We have a number of speakers who have already signed up to make comments during the Open Public Forum. But for those of you who have not had an

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opportunity to sign up to make a statement or a comment at that public forum, please feel free to go ahead and sign up for that now and we will work you into that session. You can sign up out there in the lobby, and we will call on you at that point.

Then we'll have lunch, and after lunch we'll have those two moderated sessions with a number of esteemed outside panelists. The first will be focusing on broad issues about whether we're on the right track with our proposed national strategy. And the second moderated session will delve into active postmarket risk identification and what this means for the wide array of devices that FDA regulates. And, finally, we'll close the day with a public comment period.

So without further ado, I'd like to introduce Dr. Jeffrey Shuren, who's the Director of the Center for Devices and Radiological Health, and he'll open our session today.

DR. SHUREN: Thank you, Anita.

Good morning and welcome. It's exciting that we have so many people both here and on webcast for a four-day public meeting. I emphasize, four-day public meeting. I empathize, because I'm sure the last thing you want in your life is more meetings. So we truly appreciate the fact that you're willing to commit the time and effort in what we consider absolutely critical discussions, because this is an aspect of our mission, postmarket surveillance. That is critical to our success in protecting and promoting the

public health. We cannot do it. We cannot succeed unless we have a strong and collaborative postmarket program, and that's what these next four days are all about.

So seeing such a great turnout really signals to us the interest that you have in working with us to strengthen our postmarket system so that we ultimately have what we envision as truly a national medical device postmarket surveillance system, a program that can quickly identify poorly performing devices, accurately characterize real-world performance, and facilitate device approval or clearance.

For the most part, we know that our current postmarket surveillance system has served the American public well thus far. However, our current surveillance system has important limitations and medical devices, particularly in the postmarket setting, present unique challenges, as compared to drugs and biologics, due to the greater diversity and complexity of medical devices, the iterative nature of medical device product development, the learning curve associated with technology adoption, and the relatively short product life cycle.

We recently posted an outline online of what we think we could do to strengthen the postmarket infrastructure for medical devices. In order to appreciate the areas we want to target and to figure out how we can work best together, I think it's important to understand the limitations of our current postmarket surveillance system.

Most of our limitations stem from the fact that the current postmarket system doesn't consistently collect quality data in a timely fashion. This creates challenges for the rapid identification of under-performing devices in the marketplace.

When data do exist, meaningful evaluation may be limited due to the following: the absence of identifiers or other established data standards; inconsistent coding; limited longitudinal follow-up or underdeveloped methodology that makes it harder to combine data from disparate sources and to develop longitudinal clinical profiles.

Even where the FDA requires manufacturers to collect postmarket data to evaluate an identified safety concern, it can take many months, even years, before adequate data are collected, analyzed, and communicated to patients and healthcare providers.

These individual postmarket studies can be expensive too, and a stronger system could be used to collect necessary information more quickly, efficiently, and at a lower cost.

In addition, limitations in collecting timely, quality postmarket data can make this data less useful for the development of new devices and new uses of existing devices, because the data collected by the current postmarket surveillance system may be incomplete or insufficiently robust to be used to support product approval or clearance.

This is an important piece to remember for medical devices.

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The technology that underpins medical devices is constantly evolving. Device manufacturers are always looking for ways to improve their products, which benefits patients and healthcare providers and can provide for a healthy industry. To the extent that we can utilize postmarket data to support premarket approval or clearance of new technology, we create incentives for stronger, more reliable data collection in a timely and consistent manner.

We think, and included in the draft document we recently posted, that we do not need a complete overhaul of our current system. As we've done in other areas at CDRH, we can make smart, tailored modifications to our programs that make most of work that's already under way.

Specifically, we can take four steps to significantly strengthen our postmarket surveillance system. First, we need to establish a unique device identifier system and promote its incorporation into electronic health records and other electronic health information. As you're already aware, in July we published a proposed rule for establishing a UDI system, and finalizing it is one of our top priorities. In fact, Congress too recognized the importance of this system when it shortened our implementation time for UDI in legislation that was recently passed.

Once we begin implementing UDIs, we must find ways to incorporate them into electronic health records and other electronic health information. This connection is vitally important, as it will ensure that at

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least basic critical device information is included in adverse event reports in an unambiguous and consistent way, and we can finally leverage the data that is collected every single day as a part of routine clinical practice, to help improve patient care and to truly develop a learning healthcare environment for medical devices.

Second, we need to promote and leverage national and international device registries for selected products. As you know, we have two full days that are devoted to exploring collaborations that can make these registries useful realities.

Let me be clear. We don't need registries for every type of medical device, nor is it feasible or sustainable to do so. And we don't want to develop a central repository of registry data. We think that individual registries should remain such, which also helps protect patient privacy by keeping that information behind a registry's firewall.

What's more important is that we work together to find the targeted product areas where it is most cost effective and value added to establish registries focused on public health need, patient exposure, uncertain device performance, or societal cost.

There are a number of ways that CDRH can be helpful here, even though we don't create or maintain registries, nor do we intend to do so. We can help facilitate the establishment of common data elements for registries. We can develop criteria that would support the use of a registry in

an FDA-required post-approval study. We can help create structures and promote transparency and good scientific process and conduct.

The third step is modernizing our reporting and analysis system for adverse events. I doubt there's one person here today who hasn't experienced the limitations of our current passive reporting system. There are ways to improve this, including making adverse event reporting a part of a clinician's normal workflow, through automated reporting as well as reporting through a mobile app.

In fact, it will be exciting, hopefully this fall, that when we're asked how can you report adverse event reports for medical devices, we can say, yeah, we have an app for that. In fact, we are hoping that, this fall, we will be able to announce the availability of a mobile app for reporting adverse events or problems associated with medical devices. We've been working on it with Boston Children's Hospital, and we think it will support increased reporting by healthcare providers and patients.

Lastly, we must advance the methodologies for evaluating the benefits and risks of medical devices throughout their life cycle. Our MDEpiNet Initiative is a collaborative program through which CDRH and external partners share information and resources to enhance our understanding of how well medical devices work. With innovative methodologies, greater and more systematic approaches and information on device use, performance and clinical outcomes, such as through active

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surveillance, MDEpiNet will help us, industry, healthcare providers, and patients make better, more informed healthcare, product design, and regulatory decisions. Tomorrow's discussion is centered on MDEpiNet and how it will help implement a stronger postmarket program.

We've outlined these four steps in greater detail in the strategy that we posted last week. And while I'm sure you'll find information in there that will help our discussions this week move forward, what's most important is the collaboration necessary to strengthen our system going forward. We cannot do this alone. Without the partnerships and pathways to share information, create new ways of collecting and analyzing data, and look at medical device safety in new creative ways, we'll continue to be limited by the constraints we experience today. And I think all of you agree that patients deserve better.

So thank you. And thank you again for coming, or for those who are participating by webcast, we truly appreciate it and we look forward to the next four days of meetings and what comes out of them.

Thank you.

(Applause.)

MS. RAYNER: Thank you, Dr. Shuren.

Our next speaker is Dr. Tom Gross. Dr. Gross is the Director of the Office of Surveillance and Biometrics in CDRH, and he's going to give us a whirlwind tour of the national postmarket strategy.

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DR. GROSS: Thank you, Anita.

Good morning to everyone. I hope you can hear me in the back of the room. Yes? Okay.

I too would like to express my welcome to all of you, express my gratitude for you coming. Those that are coming from near and particularly those who are coming from afar, even those coming overseas, thank you very much. We need your input.

It's nice to have this opportunity to begin this dialogue. It is very important to us. I can safely say that FDA does not have all the solutions to how best to conduct postmarket surveillance. We need your input. We need your commitment to help us devise the best national system possible.

Now, this graphic, which is in our strategic plan, I believe, nicely and aptly captures the complements of our national system. The upper six segments reflect our current tools, which I'll briefly touch upon. The lower four represent the initiatives that Dr. Shuren touched upon and that I'll delve into a bit more deeply in my talk.

Now, this is what I'd like to cover over the next few minutes: provide some context for medical device postmarket surveillance; touch upon our current tools, particularly the limitations; talk about our vision for a national system, and then, most importantly, focus on the initiatives that are laid out in our plan and then briefly touch upon next steps.

Now, for a bit of context. You're all aware that the Center has

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taken actions to strengthen our premarket program, through the 510(k) process in particular, and to facilitate device innovation through our Innovation Pathway program.

Now, postmarket surveillance is important in this endeavor because we believe that a robust postmarket surveillance system strengthens our premarket program by quickly identifying poorly performing products, characterizing real-world performance, and importantly, leveraging postmarket data to support premarket evaluation and potential earlier product market access.

Now, we can leverage postmarket data by, for example, using historical controls, by having that data be part of down-classification decisions, by identifying populations who might benefit from therapies, and potentially expanding label indications.

Now, for the purposes of this talk and today's discussion, we defined surveillance in a broad fashion: to include traditional means of surveillance, like spontaneous reporting, as well as observational study methods using a variety of different methods and data sources.

Many people recognize that our current system is problematic in many ways, inefficient, costly, and slow. To the extent that that's true, clinicians and patients are not optimally informed and patients may be exposed to preventable adverse events. Mandatory studies may not be optimally conducted, and certainly development of new devices and new uses

of existing devices may be delayed.

Also, there have been recent high-profile medical device issues that have continued to raise concerns, for example, externalization of lead conductors with regard to ICDs, and the high failure rates of metal-on-metal total hip implants.

Now, it should be noted, and it's quite apparent to those who are involved, that devices pose unique challenges as compared to drugs and biologics, and those unique challenges have implications for postmarket surveillance. I, for one, would argue that conducting postmarket surveillance for devices is much more daunting than for drugs because of the heterogeneity of devices, the complex components, the iterative changes throughout its postmarket life cycle. There are also some unique features about devices, such as design issues, human factors, and the learning curve, that they're unique to device considerations. And yes, there's no unique device identifier yet, but we hope to have the rule finalized by next year and move forward in that regard.

Now, for additional context, I think you're mostly aware that the IOM issued a report on the 510(k) process in July of 2011. Their second principal recommendation had to do with recommending that FDA develop and implement a comprehensive strategy to collect, analyze, and act on medical device postmarket information. We've done so in the form of the white paper that we recently issued and as a result of public forums such as

this.

The IOM also recommended that we take several other actions, and I'm happy to say that we have done so and we've been at work on these actions for well over a year now.

So, for instance, they recommended providing performance information for use in premarket review. We do that routinely with the results of our mandated studies program, our post-approval studies, and our 522 program. We are also setting up a signal management program so we can share the signals that are identified and the actions taken with our premarket colleagues. And I'll touch upon that a little bit more later in the talk.

They recommended that we inform further development and use of postmarket tools. We have done so with our Section 522 program and refined it over past few years. We've also engaged the public in programs such as our post-approval studies program. Indeed, we had a workshop last week to help us fine-tune that program and make it more responsive to our stakeholders and to the public at large.

The IOM also recommended that we institutionalize integration of pre- and postmarket data systems. We have been exploring software and other capabilities to help us do that, and we hope to engage in those activities later this year and next year.

They recommended that we expand collaborative relationships

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with non-FDA medical device data sources. We have done that in spades over the past few years, particularly in the registry environment, which you'll hear about more later this week.

And then, lastly, they recommended that we leverage peer-reviewed literature on device-related adverse outcomes. We have done that in the past. We're going to approach that in a more systematic fashion through our signal management program, again, which I'll mention later in the talk.

Now, let's focus on our current tools just briefly. You're all aware that we have passive and enhanced reporting systems. Our passive system is the Medical Device Reporting system, a nationwide system. We also get the international reports. We get several hundred thousand individual reports per year. We also get several hundred thousand summary reports per year. The reporting is dominated by manufacturers. Over 95% of our reports are from manufacturers.

We also have an enhanced postmarket surveillance system that goes by the name of MedSun, the Medical Product Safety Network. This has been in existence for a few years. Currently it's comprised of about 275 hospitals throughout the United States, who are collaborating with the FDA in a partnership so that hospitals could understand and report medical device-related adverse events and product problems. Through this network we have survey capabilities, we can do targeted clinical research, and there are also

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sub-networks that are specifically focused on device types of interest. So, for instance, we have a HeartNet sub-network that is focused on electrophysiology devices and a KidNet sub-network which is focused on pediatric device use.

Now, both the passive system and the enhanced system help us to address various, what I call, one-off issues like out-of-box failures, software glitches, poor maintenance, and the like. It takes only a few well-documented reports on those kinds of issues for us to meaningfully engage with manufacturers on potential solutions.

Now, what else do we have in our postmarket toolbox? We have mandated postmarket studies, our post-approval studies program, which had these conditions of approval for Class III devices. We have several ongoing studies in over three dozen device types. You can go to our website to find out more about those studies. They list the study status and also post the findings of completed studies.

Likewise we have a Section 522 program. This is used as a for-cause situation where there are postmarket issues that arise in the postmarket environment for Class II or III devices. We have several ongoing studies in this area, as well, in over one dozen device types. And similarly we have the study status and findings of these posted on our website.

We also have a discretionary study program. Over 60 studies are currently under way in a variety of data sources, registries, claims data,

electronic health records, and also other national systems such as the Consumer Product Safety Commission's Injury Surveillance System. We monitor device performance and do other activities that are very relevant to Center issues.

There are host of other tools that we use. Literature searches and systematic reviews are increasingly being used for both pre- and postmarket assessments. And there's a host of compliance tools that we use strategically and appropriately when needed.

Now, having said that we have these current tools, there are recognized limitations to our postmarket surveillance system. It often fails to collect quality data in a timely fashion. This is certainly the case with our Medical Device Reporting system. Data that are available are insufficient for needs. So given the lack of unique device identifiers, we only have limited use of claims data or electronic healthcare records. This has implications for the Sentinel Initiative, which I'll touch upon later.

The collection of required postmarket data is inefficient. So, again, given our mandatory postmarket studies, there's a lack of coordinated infrastructure. Many of these studies have to be done de novo, at higher cost of greater inefficiencies, and it may take months or years before the data are collected.

And, lastly, the system at times fails to be leveraged for appropriate premarket uses.

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Now, what about the Sentinel Initiative? This is an important Agency tool that's been in development for several years. It was mandated by Congress under the FDA Amendments Act of 2007. The act focused on drug safety surveillance, and so their efforts have been primarily drug focused. Currently you can access over 120 million patient records. It was developed and continues to be used for active surveillance purposes, using distributed data sources.

The Sentinel Initiative has made great strides in the use of those distributed data sources, in establishing systems to protect the privacy and security and integrity of those data sources, using high standards for scientific credibility in the development of methods, and having transparency in open-source information that's available on their website.

Having said that, there are opportunities, down the road, to incorporate unique device identifiers in claims data sources and electronic healthcare records, which form the substance of the distributed data sources in Sentinel. We can also add registry data sources down the road.

Now, importantly, the FDA Safety and Innovation Act of 2012 requires expansion of Sentinel to include medical devices. Later today we'll have a separate session on active postmarket risk identification, an expanded Sentinel, to include devices.

Now, what's our vision for postmarket surveillance, now that I've touched upon the current tools and some of the limitations? We believe

it's a system that performs robust surveillance in near real time. It uses high-quality electronic health information that contains unique device identifiers. It uses evidence generation synthesis and appraisal throughout the total product life cycle, and addresses both benefit and risk. It leverages distributed data sources using well-qualified data standards. And it augments other surveillance mechanisms.

By doing so, this can result in timely, accurate, systematic, and prioritized benefit/risk assessments; rapid identification of potential safety signals from a variety of sources; reduce burdensome costs of surveillance, and facilitate the marketing of new devices and new uses of existing devices.

Now, let's turn to the heart of the plan, which are the four initiatives that Dr. Shuren touched upon, beginning with unique device identification, or UDI.

Now, this is an example of a product label that contains unique device identification. There's a device identifier or the manufacturer make and model, production identification information, i.e., the lot number, the batch number, serial number, expiration dates, and the like. The product label is to be human readable and also machine readable. So you see a bar code there on the product label. We don't specify the machine that needs to read these product labels. It could be bar code technology or RFID technology, for instance.

Now, we believe that efforts to incorporate UDI and electronic



health information will be transformative and will open up significant amounts of health-related data to postmarket surveillance for devices. It will also enhance our abilities to conduct numerous activities, ranging from reporting on detecting adverse events, to streamlining and securing the supply chain, to facilitating premarket evaluation of new devices and new uses.

As mentioned previously, the UDI rule, the proposed rule, is out for comment. The comment period closes November 7th, and it will help to finalize the rule next year.

We are also working, as we speak, on establishing a global unique device identification database. We've done internal user acceptance testing. We are proceeding with external user acceptance testing shortly. We hope to have the UDI database set up by the latter part of spring next year.

Now, let's turn to the second initiative, which has to do with the development of national and international device registries. We're all aware of the importance of registries in capturing detailed patient, device, and procedural information. FDA currently uses registries for multiple purposes, but most importantly, to characterize real-world performance. We fostered the development of registries and registry consortia over the past several years. I would argue that we fostered well over two dozen registries in the past few years, and we've been actively involved in their development.

But we also recognize there are other government agencies who are very much involved with aspects of registry development. So, for instance, the Agency for Healthcare Research and Quality are very much involved in this space. They have set up the Registry of Patient Registries, for instance. They are also embarking on an interesting project called the Outcomes Measures Framework, which is to harmonize outcome measures across disparate registry sources. The NIH is involved with registry efforts, as is CMS. And so we're all well aware of their efforts and we collaborate with them as often as possible.

Lastly and, I believe, most importantly is that we have to recognize there are inefficiencies and burdens in developing registries. We have to develop a national strategy on how to approach registry development. And we hope that, with two days set aside for the registries workshop, we will begin in earnest a national dialogue on how to do that.

These are the items we hope to discuss as part of that dialogue over those two days. We would like to leverage experience and expertise that already exists for future registry development. It's important to establish common demographic, clinical, procedural, and data elements that could be used across registries. Again, outcome measures, how we harmonize those across registries is very important; to develop and share methodological tools; how best to link data sources, for instance; to enhance interoperability with electronic healthcare records and claims data; to

develop criteria that would render a registry eligible to support FDA-required post-approval studies. We do currently embed required post-approval studies in existing national registries. I think we need to ask ourselves what are the criteria by which we might be able to do that as we move forward on a broader scale?

We need to create sustainable business models. What are the business arguments to be made to stakeholders so they see a benefit for all in developing these national registries? We need to identify priority medical device types for which creation of national registries make sense. It's worth the investment. There's public health impact; and lastly, to adopt a registry governance structure that promotes rigorous design and use, reporting key findings, and transparency. So we're looking very much forward to getting your input on important aspects of registry development.

Now, let's turn to the third initiative, which has to do with modernizing adverse event reporting and analysis. There are five initiatives under the broader initiative that will help address underreporting, inefficient reporting, lack of timeliness, and better analysis of adverse event reports that we receive.

So we'll focus on developing automated adverse event reporting systems. So, for instance, in our MedSun program, currently there are a variety of different electronic systems that the network uses. They take out of those electronic systems producing hard copy reports, send those hard

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copy reports to us, and we have to upload them in our electronic system; not a very efficient way to conduct business. So we're developing software capabilities so we can have reporting electronic-to-electronic systems and make it much more straightforward and beneficial for all.

We're also piloting use of triggers for automated reporting and electronic health records. There have been some efforts on the drug side to do this. We're exploring efforts on the device side, where we can identify devices of interest, outcomes of interest. We can flag those reports and use software to auto-populate, from the EHR, the MedWatch reporting forms that would have that information, and then those could be, in automated way, sent to FDA for review and analysis.

The second effort we have is to increase the number of medical device reports received electronically. Currently, on a voluntary basis from low- and high-volume reporters, about 70% of our individual reports are received electronically. Currently we have an electronic medical device rule that is under revision, and once that rule goes into effect, we believe that up to 95% plus of our reports will come in electronically, again adding huge efficiencies to our system.

The third item has to do with developing a mobile application for adverse event reporting. As Dr. Shuren mentioned, we have been in collaboration with researchers at Boston Children's to develop a mobile application whereby medical device adverse events and product problems

can be reported using our standard reporting form. We can also push information out to holders of that mobile application; so recall information, new product information, and the like. We hope to have a pilot under way this fall and begin reporting later this year.

Another item has to do with modernizing the medical device adverse event database. We have a database that dates back to the 1990s. It's archaic at this point. It can't handle the massive volumes and complexity of the data that we currently have. And so we are modernizing that system and replacing it and hope to have a new system in place by the end of 2013 or early 2014.

And, lastly, we have an initiative to rapidly identify safety signals. We're using data mining software that, in an automated way using computerized statistical algorithms, will help us identify needles in the haystack. Again, over 400,000 individual reports are received per year. We cannot individually review those, so we are exploring other software capabilities to help us identify signals, and data mining is one of those. It works best for products that are best identified via codes, like device codes or problem codes.

There are other product problems that are best characterized using a narrative, and for that we're exploring semantic text mining capabilities that will be used against not only medical device reports but other data sources within FDA, both pre- and postmarket.

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And last but not least, one initiative is focused on developing and using new methods for evidence generation synthesis and appraisal. Innovative methods are extremely important. As we begin to use large population databases, as UDIs are incorporated into these data sources, that's great. We'll be able to develop capabilities on how to most effectively and efficiently use these data sources. MDEpiNet was established in 2010 with a focus on that effort.

The methods part of MDEpiNet is being headed by Harvard. There's Internet infrastructure portion of MDEpiNet that is being headed by Cornell. We'll hear lots more about these efforts at tomorrow's MDEpiNet annual meeting.

The Sentinel Initiative is also very important in terms of methods development. They have set up a system whereby we can query distributed data sources, where the data are secure and held behind the firewalls of the data holders. We can learn from that. As we develop registries, we can complement those other data sources that currently exist within the Sentinel environment. And, again, new methods will improve the efficiency and quality of decision making.

Now, what are the four other efforts that we're specifically undertaking to address methods development? One has to do with the use of quantitative decision analysis to evaluate benefits and risks. We believe that quantitative decision analysis will help make assessments more explicit,

clarify uncertainties, provide essential context to our decision making, as well as transparency. We piloted this capability by looking at when is the best time to remove inferior vena cava filters that are temporarily placed? What is the benefit/risk assessment as to the best time to remove those? And so it was an interesting exercise that gave us insight on how best to use quantitative decision making.

We can also use this tool to reliably incorporate patients' views and be an aid in healthcare decisions. We've explored its use, for instance, in obesity devices and the tradeoffs that patients have to make between acceptable risks and potential benefits.

Another area of methodological exploration has to do with evidence synthesis. Combining data from disparate sources, we are developing a framework for how to do that, to assess benefit/risk throughout a product's total product life cycle. And as part of this effort, we recognize that evidence synthesis could be made easier by the use of common data standards such as common control vocabularies, definitions, and formatting. And we indeed are going to launch an initiative on data management later this year, with the express purpose of improving our quality of data that we receive and handle within the Center.

Thirdly, we've explored a means by which to conduct automated signal detection. We've collaborated with researchers at Harvard to use software-driven statistical algorithms to do prospective active

surveillance. We've conducted some studies that you'll hear about in the registry workshop, proof-of-concept studies that we believe will make this a possibility, not only using registry databases but registries linked to claims and other data sources.

And, lastly, this year we're poised to set up a signal management framework. It's part of our strategic priorities for 2012. This will give us a comprehensive means by which to identify signals from a variety of sources throughout the Center, a means by which to prioritize those signals and to follow through with them with the necessary actions that need to be taken and to be transparent about these processes and inform the public.

So those are the four initiatives that we believe are very important, that are detailed in our plan, and we hope that this will be the substance of this ongoing dialogue that we want you to participate in.

And, again, I think this nicely captures our entire postmarket surveillance system.

And, lastly, we believe that these new initiatives will complement existing systems. Again, it involves a national dialogue. Please go to our website and provide your commentary. And we rely on you, as important stakeholders, to continue with this dialogue today as well as the next few days and beyond. We need your help. FDA cannot do this alone.

And I thank you very much.

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(Applause.)

MS. RAYNER: Thank you, Tom.

We're moving on to the next section of our day, and joining Dr. Shuren and Dr. Gross here at the table is Dr. Danica Marinac-Dabic, who is the Director of the Division of Epidemiology in the Office of Surveillance and Biometrics.

And we're going to try to shake this up a little bit. I'm going to ask some questions of our panelists. I'm going to ask some questions of all of you. And, you know, I was struck by the fact that we have lots of invited speakers who are going to come up over the course of the day and give us input and feedback on the questions that you see in the agenda and other issues. But I think it's also important to hear from those of you who are not a part of the invited panel. And we're also again interested in hearing from the substantial number of people who are participating in this day by webcast.

So I'm going to kick it off a little bit here with some of my questions, but then I'm going to ask you some questions too. So before we get started, let me just give a plug again for the e-mail address for submitting comments. If you're watching on the web, that's [cdhrpublicmeetings@fda.hhs.gov](mailto:cdhrpublicmeetings@fda.hhs.gov).

And with that, I'm going to turn to Dr. Shuren, and I'm going to just pose a question and say, you know, this is a very ambitious plan and ambitious sometimes translates to costly. So how is FDA going to pay for all

of this?

DR. SHUREN: So FDA wouldn't be paying for all of this. There are actually improvements we're making already with our current budget, quite frankly. That's improvements in adverse event reporting with our database system. I think folks know MAUDE is a clunker, and we're in the process of moving forward to replace that.

We've been making investments in the development of different methodologies. You'll hear more about that over the coming days. We've made investments, as we've talked about with the mobile app, on different ways of, maybe, automated reporting. There are things that we folded into our normal budget all along the way.

But if we think about this real system moving forward, we mentioned this is collaborative and that it really requires the pooling of resources, both human and financial, across stakeholders, and that is a topic for discussion.

We actually think there are many steps that can be taken that are actually cost saving in the long run. For example, for the medical device industry, we have company after company who may be spending large amounts of money on individual studies, that with better infrastructure in this country, sort of spreading out the cost among interested parties, we can actually reduce the cost overall for all.

So we think, in the long run, this will be eminently doable from

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a financial standpoint, but obviously finances are a constraint that we have to keep in the back of our mind on anything we do moving forward.

MS. RAYNER: Thank you.

Let me go to the issue of what seems to me to be under-reporting and over-reporting. Tom, you mentioned the several hundred thousand reports that we get every year, and yet you seem to be developing new methods to get more reports. Can you talk about that a little bit more?

DR. GROSS: Yeah, it goes under the category of be careful of what you ask for. We have to be responsive to developments outside of FDA. I think there's a real need for development of mobile applications so that reporting to the FDA is facilitated for the public at large.

Now, having said that, I'm well aware that could generate more reports. We already receive several hundred thousand reports per year. We recognize that fact, and we are developing software capabilities that will help us "sift" through the reports in an automated way, and to help us target those reports that we think may be of most value, based on coded information, based on narrative text, using data mining and text mining capabilities.

So we have to move along with the future, move along with future capabilities, but also realizing there are limits to what we can do, and therefore, we have to invoke other tools that we can leverage and really help us focus on the highest-value reports and to take action on those reports.

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MS. RAYNER: Thank you.

Danica, I'm hoping you can clarify something for me. You know, the postmarket strategy laid out several sub-bullets with respect to both modernizing our adverse event reporting system, but also the development of new methodologies for automated analysis of adverse events.

And so can you help me distinguish between what FDA will be doing differently versus the kind of automated signal detection that you'll be looking to do within the context of registries?

DR. MARINAC-DABIC: So as you heard from Dr. Shuren and Dr. Gross, the development and the investment into the MDEpiNet, I think, clearly taught the way for us to collaborate in a more formalized fashion with experts outside of the FDA. And by that I mean our collaboration is going to go beyond funding the ad hoc studies to address a particular question, a research question or a surveillance question that we might have at that point, but clearly strategically think about the ways of how this is going to really, truly function as a network.

So just to give a specific example, as we develop innovative methodologies for evidence synthesis, this is going to help us not only address a particular research signal but take advantage of many, many different data sources through which FDA historically didn't have access to.

So in addition to the best repository of the data that we have in

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the premarket setting, on the way of how devices perform in a highly controlled clinical trial setting, we're going to be able to add to that the information that resides in the registries, that resides in other data sources, again keeping in mind that we would like to use the distributed data network concept and couple that with the expertise that resides in our academic sites that will put, with us, together the conceptual frameworks of how this information should be synthesized, and adding to that leveraging the data from published literature, and even more importantly, not only relying on the data that are gathered in the United States, but really trying to take advantage of the wealth of the data coming from global resources.

So this is that type of strategic thinking that we are adding to what we currently have been doing, rather than addressing ad hoc and opportunistic approaches that we used in the past.

MS. RAYNER: Thank you.

I'm going to steal a page from the questions that are going to be posted to the panelists later, and I want to ask all of you in the audience to speak to these folks here who are among the primary architects of this plan, and tell us, what score would you give us? Did we hit it? Did we nail it? Did we miss things? Where do we need to focus our emphasis more or less?

I'd like to ask anyone who's interested to come up to one of the microphones there and offer an opinion. And if not, I might even come down into the audience, and you don't want to be sitting on the aisles, if that's the

case. So don't be shy.

(No response.)

MS. RAYNER: Oh no. All right, I'll give you a couple more minutes to think about it.

But in the meantime, maybe you have questions for Dr. Gross, Dr. Shuren, and Dr. Marinac-Dabic. Anyone? Or some questions from folks who are watching via the web.

DR. NORMAND: I can't stand it. It's Sharon-Lise Normand from Harvard Medical School.

I had a question, and my question relates to the ability to -- industry to provide data. What are issues regarding the combined ability, the antitrust types of things, the mixing and using data from the premarket setting to the postmarket setting?

It seems to me there's a wealth of data that industry has that would be very informative to them, but also to their competitors. And I'm just asking this from a scientific standpoint. In an ideal world, we would want to be able to utilize all of that information simultaneously. So I just wanted to get your sense of the ability and any barriers you see to that. It would be nice if industry could also speak to that particular issue as well.

DR. MARINAC-DABIC: All right, Sharon-Lise, I'll try and I'll start actually.

So Sharon-Lise, as you know, we've started using some of the

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aggregate data in some of the evidence synthesis projects, and I think that certainly is the area where we are going to continue. Much of that data is available through our summary of safety and effectiveness, and I think there are valuable additions to the current practices that we've been applying in the past, really by adding that information across different classes of devices and in trying to do develop the methods of how that can be utilized.

We also started engaging industry in thinking of what else can be done in terms of the patient-level data and how much of that can be utilized. So there is currently one pilot project underway, when we are engaging one particular industry with regard to thinking about how much information can be, in fact, added by combining the information if it's premarket, post-approval studies, and beyond. Again, we'll see how much we are going to progress in this and I think, you know, hopefully other industries are going to join.

Maybe Dr. Gross and Dr. Shuren can add to that.

DR. SHUREN: Well, you raise a great question in that, you know, some data that will be informative may also be containing confidential information, maybe proprietary, and we very much want to protect that kind of information. But at the same time you want to be best able to leverage it. And this is an opportunity for us to talk about different models for being able to aggregate information in a way that protects what's confidential so that a competitor doesn't get it, but it also assures patient privacy as well.

You know, when we talk in other scientific realms about sharing information, there have been structures created that allow for information to be shared that may provide marketing advantages to different manufacturers if the others were to have it, but are provided into, if you will, a safe space with people -- so none of the competitors see it. The people who use it can't actually provide any of the proprietary data out, but the knowledge that's generated out of it, which is more of a public good, a value to all who participate, that isn't made available.

You think about, in the regulatory science space, where we can pool information that's propriety and develop new tools, that same kind of approach can occur with data in the postmarket setting. It's a question of do we want to build that kind of a structure to allow for that safe zone for being able to use proprietary information but not let what is truly confidential go out to others who shouldn't have access to it?

MS. RAYNER: We have a question from the audience, a second one. Good.

DR. KRUCOFF: It's Mitch Krucoff from Duke. And I can't let Sharon-Lise stand alone, even though we may come back to this later in the panels.

But I think, particularly for this morning, maybe sitting here thinking about how big this stage is, we're not only talking about partnering organizations and pooling data from different languages, but even



potentially, from CDRH's point of view, from very different spaces. Most of what we heard this morning were some cardiovascular examples which, as a cardiologist, I'm happy to hear, but we know that you guys regulate a lot of other devices.

So is there some sense or plan as to how the specific areas of interest, device areas, organizations of interest, and the legalities and ethics of partnering, is there a resource that is going to try and direct specific device areas or conduct important issues, like how partnering organizations would contract, or the ethics of information sharing, along the way?

DR. MARINAC-DABIC: Under the MDEpiNet umbrella, we are thinking about the gap analysis, in terms of where are particular questions, particular areas of need, particular strategic areas where we need to focus more.

Although you've heard some examples from cardiovascular, during these two to three days, we're going to hear much more about other devices such as orthopedics, for example, where I'm sure you're aware of our efforts to build the International Consortium of Orthopedic Registries as a great example of how something that had been identified as a priority area for our Center evolved into something that is really, really now involving 15 nations with 30 international registries being part of this, combining together the information from 3.5 million procedures.

So these are the type of efforts that we are conceptualizing

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currently through the MDEpiNet framework. There is going to be much more discussion about, strategically, how we're going to tackle different device areas such as, for example, implantables, aesthetic devices, diagnostic devices, and the like because they all will require -- they're all in different stages in terms of methods development, and they all require the particular specific look into what is needed.

So I would like you to think about strategies like this today, tomorrow, and all these four days and beyond, as the areas where we need to start thinking about this national strategy. This afternoon is going to be a perfect example of when we're going to start addressing these questions, gathering the input from the wide variety of stakeholders.

MS. RAYNER: Please.

DR. RISING: Hi, good morning. Josh Rising from Pew Trusts.

One question I had is I'd be interested in hearing Dr. Shuren and others talk about how this effort integrates with some of the other major initiatives happening at CDRH. And I think, in particular, the quality initiative has some direct relationships and potential synergies with the improved postmarketing surveillance landscape. And so I'd be curious to kind of hear the panel's thoughts on how some of these other efforts are going to be integrating together.

DR. SHUREN: A very good question. Let me hit on a few. You had mentioned from the standpoint of quality. One of the challenges that we

face currently, today, is that problems that may be seen in the production of a technology or in its design may not show up until we have more experience and particularly real-world experience. Too often today we may have to see a large patient population exposed before we have that information.

One of our efforts for assuring high-quality devices is that if we can get that information more quickly and feed it back to companies and to users, we can actually, if you will, assure the quality of that technology on the market, as opposed to engaging in some of the bigger recalls that we've seen today.

The second area is on the premarket side. Because of limitations in the postmarket systems we have today, it makes it much more challenging to rely on those systems, if you will, as sort of a pressure release on what we may need in the premarket setting for a product to come on the market.

Now, there is a regulatory standard for a product to get on the market in the U.S., but in determining that balance part of it is, if we don't have, maybe, every little piece you'd like to have premarket, do you have a system that would allow you to get that fairly soon postmarket? If so, you might be able to move that needle on an evidentiary standpoint a little bit off in the postmarket setting than you have in the premarket setting.

That is a question that actually we're going to start to tackle as part of our next look at the Innovation Pathway. Folks may know that when

we rolled out the most recent version -- we called it Innovation Pathway 2.0 -- we developed that with outside experts. We had established an Entrepreneurs in Residence program, and that started to build the new pathway.

We're about to launch the next Entrepreneurs in Residence effort in the coming weeks, and one of the areas we're going to focus on is this issue about postmarket and how we can strike the right balance between premarket and postmarket, which is a nice connection between the strategy that we've just put out and the work that we've doing on the premarket side, particularly through Innovation Pathway.

MS. RAYNER: Thank you.

We have another question.

DR. NAFTEL: Hi, I'm David Naftel from the University of Alabama at Birmingham.

So everything you've presented this morning sounds so, so good, and it really sounds appropriate. Now, what I wish I were seeing at the same time was a second big screen where you were leading me through a real example of MDRs, what you want to learn postmarket. Some device life cycle, you know, a real example, I would've loved to have seen that. Of course, that's what you're trying to create.

But as I'm thinking about that, I'm back to what Sharon-Lise said, and that is we've got some real problems about what a company is

willing to show to the public, and it seems like you're in a really difficult place, trying to be transparent, at the same time having this safe zone where everybody's putting information in to you, but you've got to judge what can you show back to the public and what do you have to keep behind closed doors.

And I have no answers. I just respect you for trying to deal with this challenge. I'm not sure how you can pull it off, to keep companies happy, but let the public see, oh, that device is really having problems. We need to perhaps look to another device.

So I really don't have a question. I just feel your pain.

(Laughter.)

DR. MARINAC-DABIC: Well, just one comment with regard to this question or comment is that there are a number of examples. When you go through the actual report, through the white paper, again, without going into specifics on what is the company or what is the device, there have been some examples on how we compare and contrast the current system and what the new system is going to look like. And we try to capture the examples with regard to premarket/postmarket balance, signal identification, labeling expansions. All these are really innovative ways of addressing these issues that we haven't used in the past.

So maybe as these four days progress, we'll try to utilize more examples in terms of what we're theoretically talking about and what we can

actually show in everyday practice.

DR. SHUREN: Let me add, too. You know, the issue has been raised about data that maybe is in the FDA's possession, if you will, or industry's possession, but a lot of that is coming to us premarket. And even postmarket we get information, what we do with it.

I want to put on the table a massive inefficiency that we have in our country today, which is that information and knowledge is generated every single moment in this country, in a doctor's office, in healthcare facilities, and that information we don't have a good way of capturing and leveraging. That's, if you will, where all the real action is happening from the standpoint of the use of the technology.

And one of the things that would be great to talk about -- it is something, I will tell you, we're teeing up with, in the context also of the Innovation Pathway, is how to better incorporate, if you will, what we're calling clinical research as a part of clinical practice.

So we're always getting that information that's informative from a research standpoint. But until we actually put it in a way that is efficient for practitioners, we'll never get that information in a way that we can use to better inform improvements in technologies, better use of technologies, and assure that the technologies that come to market truly remain safe and effective and of high quality.

I'd actually see that as the higher challenge than what we may

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do with medical device manufacture data, because in reality the mechanisms for assuring protections and having the legal structures to do that, those have already been worked out in other settings. We're actually replicating it right now in a regulatory science field, which will include some of the things we're talking about today. But what happens in clinical practice is probably the bigger challenge to go after and, if you will, may actually have the biggest bang for the buck.

So I just want to put that out there. That's not a question or a comment. It's something to think about.

MS. RAYNER: Thank you.

The next question.

DR. LEWALLEN: Hello, my name's David Lewallen, and I'm here from the American Joint Replacement Registry, and I want to begin first by congratulating FDA on what looks like, I think, a very thoughtful and outstanding way to approach improving postmarket surveillance. From the brief review we've had of the materials, it looks like a lot of work has gone into this, and I want to congratulate you on that. Of course, the problem is the devil in the details, trying to achieve the things that are laid out in that template, and that's where my question comes from.

We've already built a multi-stakeholder governance and model for our registry. We have industry involved with private payers and physicians organizations, and we've rounded up all the cats and have them all

in one room.

The question that we have, given our real interest in improving postmarket surveillance and trying to cooperate in this effort is how do we do that with you? How do we develop and understand what would be helpful to FDA for its postmarket surveillance efforts, and then somehow submit a plan for doing that, that we can in some way be told is acceptable before we commit great resources on our side towards building that? And I'm wondering if you have in mind some process for this.

I think that'll be important to our registry. It may be of interest to other groups too, as they try to struggle with the various issues that have been raised already about cooperation by industry and others.

DR. MARINAC-DABIC: So thank you, Dr. Lewallen. This is a really great comment, not only because of the compliments you have given us, but also that it's almost – as you know, we are already entering the implementation of the plan, it is really an exciting way of thinking of what we can do next and how this is going to be implemented.

You know, a lot of work had been done, as you know -- I'm going back to the MDEpiNet -- in trying to formalize the partnerships, for example, and we started with expanding, with setting up the coordinating centers - Methodology Center in Harvard and Infrastructure and Center in Cornell. Now, we're expanding to other stakeholders'. We're also expanding professional societies' partnerships.



So my expectations for these three days are going to be that, hopefully, at the end of them, we are going to have the clear set of directions on what the next steps are going to be. I think that this is why, in fact, we are holding this meeting, so we can pool together the national thinking behind what the implementation of this is going to look like.

So we are open to many different ideas of how this is going to work. I think what you're going to hear from us during these four days is going to be that we would expect to have clear timelines in terms of the implementation. But we are open to many different models of how this is going to work. We may present, tomorrow, some of the business models that we put together, and also during the panels we're going to discuss others, but again very open to the suggestions from this forum.

MS. McCOLLISTER-SLIPP: Hi there. My name is Anna McCollister-Slipp, and my company is Galileo Analytics, but I'm here as a Type 1 diabetes patient advocate.

And I guess one of the questions that I have -- and my apologies that I haven't read through the new report yet -- is that I'm hoping that you're going to tap into some of the data that all the manufacturers are already collecting that isn't really being shared with patients.

I mean, for me, I make minute-by-minute, hour-by-hour decisions based on the data that I receive and the functionality of my insulin pump, my continuous glucose monitor, and my blood glucose monitor. And I

know at least all of the pump companies and a lot of the meter companies have the ability and almost require you to upload all of your data, all of your device data, over whatever time period it's been since the last time you updated, into a cloud-based service.

So they have lots of data that already exists on thousands, if not millions, of patients that tells you when the device failed, what the error systems were, all of this kind of stuff, and none of it is available to patients at all.

So there's this plethora of data that's incredibly rich. You can talk to the technical people and ask about trends, but they always say that it's proprietary. They won't tell you anything other than, you know, in terms of aggregate data, except for what you're dealing with yourself, in terms of your own issues that you're calling them about.

But there's extreme variances in the number of failure rates in insulin pumps and in glucose meters, and all of this stuff is left to the rumor mill amongst patients. And there's this rich treasure trove of data that the manufacturers already have, that they collect, that I know they analyze, that could be easily shared either with the Agency or, more importantly, directly to the patient so that we could use that to inform our decisions about what devices best serve our health.

So I don't know if that's a question as much as a suggestion, but there's a lot of really good data that's already out there that's already been

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collected, aggregated, analyzed, and just nobody has access to it but the manufacturers.

DR. SHUREN: That's a great point, and it should be one of those topics of discussion that we should engage in over the next few days. We've also looked at the ability to what we could do if we've been getting information back for individual patients, back to themselves, for what's collected, because we know there's a lot of interest.

I can tell you, we looked at it, and FDA probably doesn't have the ability to require that. But increasingly we're hearing from patients who want to know more about the data collected on themselves, and then in the aggregate, what does that sort of mean for the technology itself? And that is a discussion we should talk about here, within this group and in the months to come.

I want to build on that, too, because it goes back to -- I wanted to follow up from David Lewallen's comment. In our strategy that we put out there, I think you'll notice that we talk about a national medical device postmarket surveillance system. Nothing actually says FDA's postmarket surveillance system. We talk about things that we have.

What we also want to put on the table and maybe make clear is that we're not talking about a system that's here to disturb FDA's purposes. We're really talking about, if we're working together, a system that is serving all of our various needs, of which we are just one stakeholder amongst many.

We have certain interests in things we need to do, but so do patients, so do healthcare providers, so do companies, and how actually are we able to put together that system that's going to serve the variety of different needs?

We even want to put on the table, from a governance standpoint, are there certain aspects here that we should be thinking about, a much more broader collaborative kind of governance structure for some of these aspects, where there are decisions that FDA will need to make and we make it as a regulator? But quite frankly, some of the uses of information and systems maybe are ones -- and what we do with it, are ones that discussion should occur across a number of different stakeholders.

And you just sort of triggered that I want to make sure everyone is aware that this discussion isn't just within the context of an FDA system for FDA needs. This is about a national system for national needs of the various stakeholders. And what you put on the table is an expressed interest that we have heard repeatedly from patients.

MS. RAYNER: Thank you.

DR. GROSS: Maybe I can just add also that patients are obviously a very important stakeholder. And so we are responsive, we're trying to be responsive to their needs, i.e., developing mobile applications, so that patients and healthcare practitioners can report medical device problems and adverse events much more easily. We're interested in patient-reported outcomes, including that, for instance, in clinical trials, so hearing

from the patient directly about what their experience is with a device or another medical product exposure. I mentioned quantitative decision analysis and patient preferences. What are the tradeoffs in terms of risk and benefit of therapies?

So there are several avenues, several programs, where we are directly engaging patients because they're a critical, if not "the" critical, stakeholder in all of this.

MS. RAYNER: Thank you.

As much as we've been talking about advances in technology, we still seem to have some gaps, including the inability to efficiently receive comments and questions from those watching via the web. But we've bridged that gap thanks to Ben Eloff in the Division of Epidemiology, who is going to ask us a question that actually comes from someone who is watching via the webinar.

DR. ELOFF: Yes, I have a question from our online audience. Gregory Lange of M2S, Incorporated, asked can the panelists comment on their plans to collaborate on the postmarket surveillance system with other agencies like CMS, AHRQ, PCORI, et cetera?

DR. MARINAC-DABIC: All right, I'll start.

We have actually a great track record of working closely with our sister agencies, NIH, AHRQ, CMS, in many different capacities. We have worked together on a number of research projects. INTERMACS, for example.

The INTERMACS registry is a great example of collaboration that started with the initial effort that was funded by NIH with close collaboration with CMS and the FDA. And today that's a great data source that helps the FDA not only to receive the adverse event reports coming from the registry, but also recently became a vehicle or platform for nesting the mandated post-approval studies in the area of ventricular-assisted devices, for example.

We've also worked very closely with the Agency for Healthcare Research and Quality in a number of ways, supporting and providing ideas for the DECIDE and CERT networks. We also collaborated as co-authors and authors of the chapters in r guidebook on registry development. They serve on a steering committee, for example, of a number of our initiatives. We also serve on steering committees of their initiatives, including the TJR-FORCE registry, for example.

With CMS, increasingly we are exploring the ways of how we can work better. And the establishment of TVT Registry, for example, was a great example in terms of how all agencies work together in light of recently approved transforming technology and how the national registry had been developed through the leadership from the American College of Cardiology and Society of Thoracic Surgeons.

But, really, without close collaboration between the FDA and CMS and AHRQ and NIH, this would not have been such a great success, because we added additional strengths, we added additional sticks

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sometimes, if you will. I think it was a great collaboration.

So we envision that, through this national postmarket surveillance strategy, there is going to be a prominent role for our sister agencies to work with us.

Again, as Dr. Shuren mentioned, this is not the FDA national postmarket surveillance system. This is the nation's postmarket surveillance system, and without these pillars of our national surveillance systems, you would not be able to march forward with this.

MS. RAYNER: Anyone else want to add to that?

(No response.)

MS. RAYNER: We have time for one or two more questions or comments.

DR. MACK: So this is more of a comment. I'm Mike Mack from Baylor in Dallas.

And regarding Jeff and Danica's comments about this is not the FDA's, per se, registry. So with the TVT Registry that Danica has been alluding to, it has created a national registry that has multiple stakeholders, and each of those stakeholders has a different requirement or need from that registry.

So the FDA postmarket requirements are different from the premarket requirements, are different from the CMS requirements, are different from the industry sponsor's requirements, are different from the professional societies' in terms of comparative effectiveness research and

appropriate use criteria, et cetera.

What I'm leading to is we have developed a registry that is attempting to be all things to all people and gets to the point of being very burdensome. I mean, right now, it's a 480 data field entry database. And sometimes it's like crossing a zebra and a horse; you get a zorse that kind of doesn't look very good, in an attempt to satisfy all stakeholders and meet all the needs.

So it's a very innovative process, and it's attempting to be all things to all people, but it's easier said than done, and creating something that is user friendly, doable, and not unduly burdensome to clinicians and their teams doing data entry, yet satisfies the safety and effectiveness needs of the FDA and the reasonable and necessary requirements of CMS, et cetera.

MS. RAYNER: May I ask a follow-up question? I'm teasing, actually. What are your ideas for how to address those inefficiencies or how to improve the situation?

DR. MACK: So it's a constant work in process, and I must say that it's been a partnership and a collaboration that is unprecedented. The folks here in the room, from both the FDA postmarket surveillance group, to the premarket group, to the folks at CMS, to the folks at DCRI, to the industry sponsors, everybody's working through uncharted waters here, and everybody realizes the problems. There's a lot of unintended consequences that come up with decisions that are made, that are difficult to work through.



But I think the openness to think out of the box and to realize that we are doing something different and trying to make it better, there is no one pat solution to it. Every week it's a different problem, it's a different obstacle that has to be overcome within the confines of current regulations, et cetera. So there is no one pat answer or solution to this, other than everybody working together and being open. I must say that the willingness of people to be available constantly to figure this out is applaudable.

DR. MARINAC-DABIC: So can I just add one more to that? Because there is no integrated and coordinated postmarket surveillance system in the country, perhaps today we need a registry that has 400 data elements. As we develop the postmarket surveillance system strategy, and as electronic health records are really fully integrated and embedded, and there is coordination and utilization of this data by many stakeholders, ultimately I can see that in the years to come, we may not need to collect all the data in the registry and to be as burdensome on a clinical community as we currently are, because there is going to be the linking, that it's going to work much more seamlessly than it's working today.

There is going to be the day when this not going to be reserved, the access to the appropriate data is not going to be reserved only for the best minds in the best academic sites, but really it's going to be a way where all the stakeholders will be able actually to have the access to all the appropriate data.

So you're absolutely right, there are registries and there are registries. You know, we learned that we clearly needed to collect many data elements because we're trying to satisfy many different needs. Actually, I can say that FDA added probably a lot to the data collection tool. It would've been less if it wasn't for the mandated post-approval studies. That's why I feel so compelled to maybe explain why we have this many at this point. But, again, I see the path forward where these data sources are going to be less and less burdensome as we work together.

MS. RAYNER: Thank you, Danica.

Please, time for one more question.

DR. KRUCOFF: Actually maybe just a comment to follow on, and hopefully we'll spend or have a lot of time this week to continue to talk.

But I think what Michael is pointing to is real important for us to step back and recognize, that if the objectives are to create registries in the postmarket that serve the whole ecosystem of all stakeholders all the time, we're talking about an impossible task.

On the other hand, if we recognize that there's a certain core minimum of information, information quality, information common definitions, and information flow, that can come pretty naturally from the offices or where the action is, from a cath lab, from an operating theater putting in hips. That is a core minimum that we could universalize and stabilize as a flow.

Then, for a particular manufacturer, for a premarket IDE, they need to do a little more than that. What we've created is an environment where they get basically the whole first periprocedural index hospitalization for free, and that they have to do a little more than that is a whole lot less than they have to do now.

So I think if we think in terms of layering information and needs, we can actually integrate the whole ecosystem of stakeholders around a common core of information. That's not all things to everyone, but it is something for everyone. And that kind of thinking, I think, would give us a much more realistic starting point and a much more universal construct.

DR. SHUREN: It is an excellent point. And to build on that, our experiences here with TVT and in other places also have been pushing us to go back and revisit our expectations, because you can't be all things to all people, also, if your expectations are too broad from all stakeholders. And so we're willing to go back and say, you know, maybe we don't know this as much, or we don't need that, this will be good enough, because overall we'll get more out of this system than the way we're doing it today. And that is a discussion that we're having inside the FDA, inside CDRH, right now.

DR. GROSS: Right. And I appreciate those comments, too, because I think you're exactly right. I alluded to it in my comments, talking about the postmarket plan, sort of modules that are usable across all registry efforts. Right now it's sort of a one-off enterprise. Everybody's doing heavy

lifting. I don't think there's a need for that. Also, when you burden a system like that, the timeliness of the data, the quality of the data are adversely affected, I believe.

So there are real tradeoffs that we have to make in the short term, but being cognizant that the environment is forever changing. We have to be responsive to the ever-changing environment. So when UDIs are incorporated in electronic health records, for instance, that opens up a whole other avenue on how to approach issues like this.

So we appreciate efforts like the TVT Registry, the INTERMACS registry that preceded it. A lot of heavy lifting involved, lessons learned. But I think you're absolutely right, and that's why we're advocating for a national approach that won't meet everybody's needs all the time, but is more sensible, and I think at the end of the day provides greater public health good. So I definitely appreciate those comments.

MS. RAYNER: Okay, just to wrap up this first session, and we're by no means done for the day, we've started the dialogue, but let me get to the sort of boots-on-the-ground question. You know, we're getting input, we want to get all of this input. What are the next steps for FDA with the plan?

DR. MARINAC-DABIC: Well, there are these busy four days, this four-day marathon that we have ahead of us, and as being on a front line of preparing these four days, if anybody tells me that there is no postmarket infrastructure in this country, I'm going to tell this is not true. The way of

how we are able to actually pull off this meeting in two and a half weeks after we received the green light to go ahead with it, was a great way to showcase how much commitment there is in our country to help us get where we would like to be.

People were canceling their clinical appointments, calling from overseas, coming from overseas, receiving a notice two days before the meeting that they're going to be on a panel, and 98% of the speakers that we originally invited actually showed up and are going to be part of this.

So in that spirit, I would like perhaps to just conclude this session, that these four days are going to be crucial for us to summarize the input, not only on what are the elements of the postmarket plan, but what the implementation strategy is going to look like.

What we can promise on our side, this is our highest priority, and we will work with you every single day. We'll be open to comments, we'll be open to ways of how we can work better, and based on the input that we receive these four days, we are going to put this together as the national system for postmarket surveillance for medical devices.

DR. SHUREN: And then we're targeting to put out the informed strategy by -- our deadline is the end of the year.

DR. MARINAC-DABIC: The end of the calendar year.

DR. SHUREN: Calendar year.

DR. MARINAC-DABIC: Yes.

DR. GROSS: Yeah, and again, I just want to reiterate that it's not FDA's plan, but you should all feel ownership of this plan. We don't have all the solutions. The solutions reside out there as well. So it's really important that you feel that you have some ownership of this plan as well.

MS. RAYNER: Thank you, all of you.-

DR. MARINAC-DABIC: Thank you.

MS. RAYNER: I just thank you for starting this day with -- and all of you with your questions and comments, I think we're prime to move ahead smartly, and the next session we'll have our Open Public Forum. Several of you have signed up to make a statement or comment. If you have not yet signed up, you can sign up in the lobby during the break.

We will reconvene in about 15 minutes, which is 11:05. Thank you.

(Off the record.)

(On the record.)

MS. RAYNER: We're about to start the Open Public Forum section of today's meeting.

This section of our day is going to be spent hearing from individuals who have signed up to provide comment and input to the Agency in advance, and I have the names of several people. If you wish to have that opportunity and you have not yet signed up, you may still do that. We will probably have some time to accommodate you this morning before lunch.

You can sign up out in the lobby.

With that said, I am going to ask Dr. Brindis -- is Dr. Brindis here? Great. Dr. Brindis, would you like to offer us your comments?

DR. BRINDIS: Well, thank you.

First of all, I apologize a little bit for the formality of these comments, and I look forward to the informal discussions over the next four days.

My name is Ralph Brindis. I'm here today in the capacity as the representative of the American College of Cardiology. I have served as the previous chief medical officer and the chair of the National Cardiovascular Data Registry, founded in 1997, and also have served as past president of the American College of Cardiology.

The College is a 40,000 member, nonprofit medical society composed of physicians, nurses, nurse practitioners, physician assistants, pharmacists, and practice managers, and bestows credentials upon cardiovascular specialists who meet its stringent qualifications. The American College of Cardiology is a leader in the formulation of health policy standards, guidelines, and is a staunch supporter of cardiovascular research.

The College also provides professional education and operates national registries for the measurement and improvement of quality care. Our experience with registry operations and patient care informs the views we offer today on the FDA's recently announced national strategy for

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strengthening the nation's postmarket surveillance system, and we greatly appreciate the opportunity to share these thoughts.

First of all, we commend the FDA for recognizing the need for a refocus on our overall postmarket surveillance strategy. As cardiologists and cardiovascular specialists and cardiovascular surgeons and members, we know too well the problems that can result from device failures and our current inability to truly track patients with implanted devices that have sometimes proven problematic. The current system isn't perfect, but ripe for opportunities in improvement.

We truly congratulate the FDA for its proactive vision for postmarket surveillance as outlined in its document, Strengthening Our National System for Medical Device Postmarket Surveillance. And also I'll congratulate you for convening these conferences this week, seeking both stakeholder input and validation of your vision.

Today's postmarket surveillance system relies too heavily on a system of passive event reporting, generated by busy clinicians who may not understand what to look for, how to complete and submit adverse event reports to industry or the FDA. Though passive event reporting offers important signals, problems with underreporting, inaccurate and incomplete reporting, and even duplicate reporting represents substantial challenges for meaningful interpretations despite its excellent signals.

While modern at the time of its creation, the MAUDE database

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has a significant number of flaws and is generally considered antiquated by those expert in postmarket surveillance. This system must be modernized if it's to keep pace with the 21st century technology that it's charged with monitoring. We look forward to the day when the country has the envisioned postmarket device surveillance program that is fully inclusive of the designated implanted devices, that offers ready patient and device identification, that also makes HIPAA compliance, and that functions in near real-time fashion, offering true protection for our patients while maximizing the opportunities for patient access to novel and innovative technologies.

Since 1997 the ACC has been collecting data on a number of a cardiovascular procedures through the National Cardiovascular Data Registry, the NCDR. The NCDR was originally launched as a result of ACC's exploration of various strategies for collecting and using clinical data to improve cardiovascular patient care. The mission and outgrowth of this effort focused on quality patient care through standardized measurement of clinical practice and patient outcomes. Today, more than 2,200 hospitals and 1,000 physician practices nationwide participate in the NCDR.

As a trusted patient-centered resource, the NCDR has developed clinical modules, programs, and information solutions that support the area of cardiovascular care, where quality can be measured, benchmarked, and improved to make differences in patients' lives.

As we have grown, its mission has evolved and changed. While

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its primary focus remains in quality improvement, the NCDR data is used for a variety of purposes, including comparative effectiveness research and now postmarket surveillance. The NCDR captures the real-world application of FDA-approved devices, giving us insight as to how devices are used and function outside of the clinical trial setting. Based on the College experience, we can unequivocally say that national registries have a vital role to play in a nationwide postmarket surveillance system.

We do have some concerns about how such crucial efforts will be funded, given the not-insignificant expense in developing and maintaining such clinical data repositories, along with the nation's need to ensure the sustainability for the registry's existence, given the key roles envisioned for postmarket surveillance.

Over the next few days we'll have the opportunity to discuss the benefits and weaknesses of registries and the regulations affecting registry involvement in postmarket surveillance. We applaud the FDA's inclusion of registries in their strategy for postmarket surveillance of medical devices.

The College also supports the development of the unique device identifier. We look forward to providing the FDA with formal written comments on the proposed regulation, but we would like to highlight how important the UDI would be in helping us to protect cardiovascular patients, especially those with implanted devices. The linkage of the UDI to clinical

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information and its ready availability to clinicians will be critical towards this end. As such, the ACC has already begun discussions as to how to best incorporate the UDI into the NCDR in a manner that will provide participating hospitals and physicians with the necessary information to furnish the highest quality patient care.

The ACC supports the expansion of the Sentinel system to include medical devices, during the debate surrounding the passage of the FDA Safety and Innovation Act, and is very pleased to see the FDA has included Sentinel as part of its strategy and overall plan for a true postmarket surveillance program. We look forward to working closely with the FDA and others to fully incorporate the NCDR data into this exciting new safety program.

Overall, the ACC strongly supports the FDA's recent strategy in developing a true market surveillance system that's focusing on establishing a UDI system and promoting its incorporation to help electronic health information; promoting the development and full utilization of the national, professional, and international device registries; the modernization of adverse event reporting and analysis; and the development and use of new methods for evidence generation and synthesis.

We look forward to working with the Agency to implement these four key strategies, in particular, to help fully harness the power of our registry portfolio in accomplishing these crucial and lofty goals.

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Again, thank you for the opportunity to comment and to actively participate in the next few days of these discussions.

MS. RAYNER: Thank you, Dr. Brindis.

Next, is Dr. Paul Brown here? Dr. Brown.

MR. BROWN: Good morning. I'm actually not a doctor, so Mr. Brown is fine. I thought I actually signed up for the public comments, but I'll be brief in my comments right now, if that's okay.

The four actions, you know, what's not to like about the four proposed initiatives. I found a couple things. I'm concerned in the details on the -- when you had an example. I think it was in the box.

MS. RAYNER: Mr. Brown, I'm sorry.

MR. BROWN: Yes?

MS. RAYNER: Are you representing yourself or an organization?

MR. BROWN: Oh, I'm sorry. I'm with the National Research Center for Women and Families.

MS. RAYNER: Okay.

MR. BROWN: I'm concerned with the off-label use, the example that was given Box C-2. I'm worried that it'll be used to skirt clinical trials. As FDA is very well aware, there are off-label use problems where promotion for medical products are used. If we're using this system, I think it's an incentive to go around the clinical trials. So I'm concerned about the

off-label use provisions.

I'm also concerned who will have access to registries, on the registry databases. On the metal-on-metal hips, the information came from Great Britain's databases, I believe. We do have private databases here in this country, and I'm just concerned that patients, and especially the FDA, may not get all of the information if it's not necessarily a government-run registry. I know you want to bring in as broad a number of registries as possible, but that's another concern.

Another thing I noted was that Dr. Shuren mentioned that we must make the data usable for clinicians. I think that's key. He mentioned that in the first panel. There's an article recently about high blood pressure. Apparently, clinicians have all of this information about the millions of people with high blood pressure in the files, but for some reason that information is not being used by the clinicians. So if we collect all of this data and it's not in a form that's usable for the clinicians, I think that that is key to actually making this is a usable and effective system.

Once again the four initiatives, I think, are fine. The key is going to be implementation. That's where we're going to run into some problems.

Those are my comments. Thank you very much.

MS. RAYNER: Thank you.

Do we have Dr. Kate Ryan here? National Women's Health

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Network.

(No response.)

MS. RAYNER: Okay. And apparently not.

We have Dr. Pidaparti. I hope I didn't mangle your name too bad.

MR. PIDAPARTI: No, you did not. And I'm not a doctor, either, but I'm a consultant from a medical device -- in the medical device space, from a company called Libra. We work with many, many large medical device companies, and my focus is medical devices, and postmarket surveillance is even more my focus area. And so we work with and provide services, end-to-end services, for the postmarket surveillance, and I worked with a very large company with multiple divisions over the summer to harmonize their processes.

So when I seen this initiative, which I think is very laudable and a great initiative, I found that to collect more data and sift through and make sense is very good, but can you collect more meaningful data? And how you put some best practices or standardization of collecting the data itself, I think, is also something that the industry and FDA probably should work together. Because I found that harmonization process of this company with multiple divisions, as warning letters from a different competitor of this company, there are ways where even the complaint intake has a lot of variation and is prone to error.

What we have also done is create an entire FMBA process for the complaint handling from start to finish, and with that process I found a complaint. The life of a complaint really is like a finance tape machine, where you have this tape and new information could change as new and additional information comes. So if you take that view, it's extremely important that you just don't add new information, but more meaningful additional information.

So I guess it's more like a comment/recommendation that there needs to be enough emphasis on collecting the data that is more accurate and meaningful than -- and share the means of collecting data is less error prone.

So one of the things I saw is this large company that I worked for in the summer, basically they had in one division telephone and e-mail and fax, and in another division they have a system inputting directly into their complaint handling system.

So it's not that you cannot input erroneous data in the second case, but the chances of more superfluous data being input is less, is what I found when I looked at a lot of complaints.

So I guess I will stop now, but define this to say that emphasis has to be placed on standardizing this complaint handling process, where the data collected, as it pertains to the complaint itself, is less error prone.

Thank you.

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MS. RAYNER: Thank you.

Do any other members of the audience wish to make a statement at this time? There will also be another opportunity. After we finish our two panels this afternoon, I believe we have another comment period planned. I'm going to check with Danica on timing here.

DR. MARINAC-DABIC: So I'm thinking, if there are no more comments, formal, maybe we can call for some other comments from the audience, because we still have some time. So I'm thinking, if there are those of you who didn't sign up for any formal comments, we would still like to give you an opportunity to do so within the next 10 minutes or so. And there you go.

DR. RESNIC: An open mike is dangerous.

So Fred Resnic, Lahey Clinic at Tufts University medical school.

First, I just wanted to thank the leaders of CDRH, the panel members, Dr. Maisel, for putting together the strategy document. I think it is really a hugely important step forward for those of us who are clinicians and those of us also who are interested in public health research and identifying the best that medical devices can provide in terms of improvements in patient outcomes.

I was actually fascinated with one of the latter parts of the framework document that spoke to what I think is a critical overlapping need for exploration, methods research, and policy implications regarding the



chain of what to do with a signal once it is identified. And I think that sort of everything that -- all the value of the postmarket effort comes down to how that sort of information is going to be handled. And obviously there's so much in terms of nuances of public health risk, uncertainty of the information, the timeliness of the information, the complexity of addressing the problem that may be evident in a signal. And I was hoping that the panel could comment on both the methodologic needs as well as the policy development issues around signal identification and verification and communication.

DR. GROSS: Yeah, let me weigh in on that a little bit, Fred.

So you're referring to the signal management effort, I believe. Heretofore, the way we've handled signals is sort of in a patchwork, and so we're trying to develop a framework that presents a systematic approach to identifying signals. Now, they can come from various sources, medical device reports being an important source, but other sources as well. And then to engage across the Center with subject matter experts, in terms of interpreting the signals, in terms of gathering additional information, which could help refine our understanding of potential signals. And then ultimately to work through that process and consider options and actions that need to be taken, and part of that is the issue of transparency.

And when you made your comments, it made me think of the Sentinel Initiative, which, again, has been in effect for a few years. I know

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they have grappled with similar issues. So to the extent that there are drug safety issues that need to be explored in these distributed data sources, they're trying to be very transparent in identifying potential signals and methods that they're deploying to address those signals, and it may lead to formal protocols. They're also published and are very transparent.

There is a great concern that when we deploy these systems for signal identification, that there is, if you don't do this correctly, a great chance for false positives, and that's the last thing that you want to trigger.

So there's much more work that needs to be done on the device side, much more work on the drug side that could enhance the sensitivity of systems but also decrease the tendency towards false positives, because we have to, I think, be assured that if we do identify potential signals, that they are mostly likely real signals. And there's a tradeoff in terms of how much information, how assured do you have to be before you act on signals?

So that's part of the dialogue that we hope to engage the stakeholders in, is the need for methods development, the need to understand, you know, how confident can we be of the methods that we deploy against the databases that we use to generate potential signals, and at what point in time do those signals become transparent and we work through the process? We don't have the answers to that, nor does Sentinel have the answers. And these are things that we're trying to work through, so we do

need your input in this regard. But I think those are very critical issues that we need to address.

DR. MARINAC-DABIC: So, Fred, a couple of things here. I think what Tom was talking about really are signal management and the way of how we are going to deal with a signal that had been identified, and what needs to be done to be amplified, or we can make sure that that's actually a true signal.

I think much of the discussion that we're going to have today and tomorrow, and certainly on registries the two days, is going to involve what goes into the process of us identifying the signal. How much broader and how much more systematic we're going to be now, in being able to create a system where not only the MDR or a particular literature review or a particular post-approval study, but all of these sources together and then augmenting with our external extramural arm or MDEpiNet infrastructure and also other data sources that are going to be part of the national postmarket surveillance system, how much of that is going to contribute to us being in a better situation to identify the signal sooner, nearer real time, and to do something with it.

So I think we need, as we move on with these four days of meetings, to talk about all of these buckets of what constitutes, really, signal management process, identification, amplification, signal management, and then acting upon a particular signal.

DR. SHUREN: And the only thing I'd add is we're probably talking about signal escalation on two different levels. So we're working on signal escalation from the standpoint of the FDA. I would put on the table that we need to be thinking about signal escalation from the standpoint of a national medical device surveillance system because there are different interests and different needs.

And you can even be thinking about if there's a participant in the system because there are a lot of ways of configuring it. You heard earlier about available registries and under what circumstances to participate or not participate. Part of that will go to a registry itself. The owners of that are looking at things. If you're participating, we should talk about what may be the expectations of them providing information into the more national system, under what circumstance. That's a much more meta level for signal escalation that is beyond simply what FDA is thinking about for our own internal purposes.

DR. LEWALLEN: Hi. Dave Lewallen again, the American Joint Replacement Registry. Let me just make a comment about this issue of signal or outlier identification and how that's managed in a general term.

We've had to struggle through this because we're talking, in our registry, not just about information that we will release about devices, which the manufacturers are pretty interested in, but also surgeon data, hospital data, and each of the entities have a similar concern. And it really

comes from our heroes, the cardiologists, who have taught us so much about how to do this. As we know from their literature, it's very important that there's appropriate risk stratification in some of the earlier publications, simplistically.

If you have mortality data that's listed simply by hospital with no risk adjustment, everyone here knows this data, you know, 1 through 10, you get a list of hospitals. And then if you do simple risk adjustment, suddenly the Number 10 hospital is Number 1 because of the difficult patients they take care of, Number 2 goes to last, and so on.

And so how do you manage that? And if you get data early and it shows mortality rates that may be important, but you don't have the risk adjustment yet, what do you do with that information? And it really comes down to why we do this. What are we about? Why are we doing this exercise? And it's really for the patients. It's not about us. It's to improve patient care. And what we need for patient care to be improved is changes in behavior by all of those who deliver care along the way, the surgeon, the hospital, the payers, because they incentivize or disincentivize different behaviors on the part of those entities. And then certainly the manufacturers have a major role.

But each of those entities has the same interest, that the data that's made public is fair about that. So they're not against transparency, but they have a little problem with the data simply being thrown up on the wall

and then have it misinterpreted to potential disadvantage.

So to crystallize the question, do we really want to publicly shame a hospital that's a safety net hospital, that takes care of indigent patients and has poor results because of that, for reasons that relate to issues beyond their control? Is that the kind of thing we want to do? I don't think so. And that's really what it comes down to.

So we have decided on our own, in our system, and I would argue for the rest of the folks here to think about transparency, but phased transparency. The data will eventually be public, once it's been cooked, once it's been looked at, once it's been validated in a way that people consider fair. But before that, you can have confidential data sharing.

So I get my number when it's early on, and I see that my dislocation rate after total hips is 10 times higher than the national average. It's not an answer. It's now a question. What's going on? And I can look into that using other things beyond the registry that answer for my own purposes. And maybe when the risk adjustment data comes out, it shows I'm okay because it's the mix of patients, or maybe not. But my behavior change can start much earlier than it will ever begin if we wait for data that's perfect.

So I think that kind of approach or thought process makes sense to us. View registries as a way of generating interesting questions, not coming up with the final answer, so that the questions can be posed initially in small groups, internally inside agencies, not for public view, inside

institutions or an individual practitioner's hands. And then, as it becomes more robust, eventually we will have transparency.

This is the way it's worked around the world in other national registries. They started with data that was really not very transparent. It's increasingly transparent as it goes along, and the processes are worked out and people are comfortable, and I think it's the way we have to do it.

The analogy we've used is lobsters, you know? We've got to put them in the pot and turn up the heat slowly or all our doctors are going to jump out, right? So we've got to get a process, turn up the heat slowly and let them respond to this and change their behaviors, because in the end that serves the public need. It improves care. This isn't about selling newspapers and having public shamings. It's about improving care, and that's where our focus needs to be, I think.

DR. NORMAND: I'm getting in ahead of Mitch.

DR. KRUCOFF: Only because I love her.

(Laughter.)

DR. NORMAND: Yeah, publicly he stated this.

I'm still Sharon-Lise Normand, but I just wanted to react to the comment that was just raised, Mitch. And so I'm going to throw something out and just see what people think about this.

So Dr. Gross had mentioned something about false positive rates. So I'm going to submit that I think the probability of a false positive

rate shouldn't be 1%. I think we should err on the side of saying we'll allow a higher error on that side.

And so I think we've gotten into -- when I say we, the royal we -- the postmarket surveillance, let's say, into this clinical trial thinking of Type I and Type II errors and having a certain level. And I just sort of want to throw out, and I truly believe this, we need to rethink what type of risks we're going to take. And I'm not so sure, at least if I were a patient, I'd rather have a higher probability of a false positive than to say that there was a false negative.

And so I think we need to think about those types of things, rather than saying, you know, we always say .05, we always say .1. I just really think, trading off, let's get away from the same old same old, only because that's been tradition. I think we need to think through it, and what are you really willing to trade off?

So that's what I wanted to get in ahead. I'm sorry, Mitch.

DR. KRUCOFF: Mitch Krucoff from Duke.

And, again, along the same lines, I think this whole level of discussion is critical as we gather information on a nationalized or internationalized registry basis that's safety oriented. We better be pretty clear about how we hope or plan to manage safety signals. And I think to contrast where we are today, where the media handles most of our safety signals for us, that we can do better than that.



I think understanding what creating a risk-averse environment means, when the media handles that; I think, at the bedside, understanding informed consent, what information physicians actually have to tell patients about off-label use or on-label use; these are the areas that, frankly, I think are going to come back to exactly the same thing we were talking about before.

There will be a core minimum amount of information that matters to all stakeholders, and that would be really smart to focus on how that information is aggregated, how it's governed, how it's analyzed, even by wonderful people up at Harvard. You know, a short term, particularly for a permanently implantable device, there may be short-term events that create a signal. But 3 or 5 years or 10 years down the road, maybe that signal was counterbalanced, so we've got to be smart.

At the same time, there are going to be individual stakeholder needs that are different, and we will not solve all things for all groups and all stakeholders without them putting some of their own investment into their pieces.

So if we try and make it all things for all people and manage safety information to make everybody happy, then we'll be, 10 years from now, still talking about it and the media will still be creating a risk-averse environment for us. But if we can be smart and see first what is it that we all really want to know, what is a signal level that would make all of us want it to

be known, and is it device related or operator related or adjunctive therapy related or risk patient subpopulation related, those kinds of things we could create certainty about in an ongoing registry environment. A signal can be identified and then quickly prospectively reinterrogated with new inflowing information. There are lots of tools here. But if we start trying to please everyone's every need from the get-go, we'll never go.

If we start by focusing on what is the core information that's critical to everybody in a signal and its management, and then each stakeholder has an opportunity to add additional layers of what -- as a physician, I might want to find out, is Dr. Brindis really doing his job in the cath lab, you know. That's different than what the FDA may want to know about a device or a manufacturer may want to know.

We can do this smartly and actually do it if we start by understanding what is the core minimum safety information, and how would we want to govern and manage how that information gets out for informed consent, for the media, on behalf of patients, rather than the way we do it now.

DR. RESNIC: I just wanted to follow up on Mitch's point. I think the other thing, in terms of the framework of signals, that I would hope maybe the audience and the participants over the next couple of days could think about is that we really need to have a pretty adaptable framework in cardiology. In implantable devices within cardiology, there are a wide variety

of adverse events that may be device related, may be physician training related, physician skill, even at steady state, but I think we have to kind of maybe use the patient-centered framework to help guide us. What would the patient want to know, what do our patients want to know? And I think that we might need to have a pretty adaptive approach that also gauges the severity of the outcome as to the comfort level with Type I errors, with false positives.

So if I'm a patient -- I am a provider, but we're all patients, as well -- I'd be very interested in having the stakeholders in this room explore a potential 25% increase in mortality with one device versus another, even if the probability of that signal were only at 80% or 90%, whereas if it were a minor complication like a radial artery, a sterile hematoma that doesn't have a long-term effect but could be differences between devices, perhaps we'd need 99% certainty that the signal was real before it would warrant the level of exploration and the resource commitment. And I think perhaps using this sort of patient-centered approach may help guide a more adaptive framework or an adaptive framework.

Thanks.

DR. SEDRAKYAN: Art Sedrakyan from Cornell.

I thought I should wait until there's a panel for all of us to talk because we're on a panel, but my colleague started talking, so I said maybe I should I add to this discussion.

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(Laughter.)

DR. SEDRAKYAN: I really feel this discussion around signal detection and amplification and acting on it is important, but I think it kind of puts -- ignores a little bit the elephant in the room, which is really building that data, the data system, the registries, which is often not about knowledge and understanding. It's about relationship and trust and ability to work with a team in a team environment with clinicians, with staff for the hospitals, with policymakers, potentially.

This is the most complex thing and would again -- Mike was talking about the complexity of these data elements growing into hundreds and hundreds of elements, that it's hard to manage. But the trust in getting everybody to agree to enter the information, I think it's really critically important. Being able to come up with creative methods to make it more efficient.

David Lewallen is struggling with the American Joint Replacement Registry. Their number one problem is the participation of the hospitals. What is it that can be offered to them so that they are part of the national system development?

I don't think we want to scare people off with a lot of the signal detection and what we're going to do, punish people or outlier discussions, when we haven't built a system yet nationally or make the first important steps to move forward in that direction.

MS. RAYNER: Ah, we've stimulated some discussion here.

(Laughter.)

MS. RAYNER: But before we go to your comments, Danica, did you want to -- I thought you were saying -- had a reaction to what Art just said?

DR. MARINAC-DABIC: No, no, that's all right, I can wait.

MS. RAYNER: Thank you.

DR. MACK: This is Mike Mack again. I'd like to respond to Dr. Lewallen's comments about risk adjustment.

Everybody knows that a medical device is a product of the ecosystem in which it's used in. And as well as the performance of the device itself, there's performance of the hospital that it's employed in, how frequently it's used, and the operator skill set, and all of that is important.

Now, the whole reason that the ACC and the STS formed their clinical databases years ago is to risk-adjust outcomes data, that administrative claims databases didn't account for this and that we all know that to level the playing field and to really have an apples-to-apples comparison, this needed to be done. And, indeed, there are very robust risk algorithms that exist that can level outcomes.

A lot of the 480 data elements I mentioned of the TVT Registry include elements that are necessary for a risk adjustment algorithm within this. So I think that we really can begin to figure out device performance in a

specific institution, by a specific operator.

Transcatheter valves. Do they do just as well when you do three a year as when you do 100 a year? We all know from the carotid stenting device literature that there is an operator-dependent thing, and that's an important thing that a patient wants to know.

So I think that clinical registries now are at a stage where we really can have true risk-adjusted data.

The other part about public transparency, the STS database now has voluntary public reporting, and almost half of the institutions and surgeons in the United States have agreed to have their data publicly reported by Consumer Reports, so that I think we are at the stage that once we get through the kinks on this, that public reporting is a desirable outcome of this and it shouldn't be behind the curtains.

DR. LYSTIG: Hi, I'm Ted Lystig from Medtronic.

So I think that the signal management perspective is something that's really quite interesting in terms of how it is not only that we find a signal but how we set up a system to act upon it and to what extent it becomes escalated and how it becomes escalated.

I am not in complete agreement with Sharon-Lise's statement about the different thresholds for safety. I think if you're going to make a decision, you'd like to minimize the rate at which you make an incorrect decision. But I think it's very important to go to what some other persons

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had talked about, the impact of that decision, whether it's something that you know that you have very good certainty about a minor adverse event versus a larger uncertainty about something that has a major impact on the patient.

But I think one way to get around this is to nest this within the larger discussion about involving risk/benefit profile and especially the benefit/risk assessment part of the initiatives that you talked about, Tom. I think that gives us a lot better sense in terms of how we should be weighting these various things, and that gets back to the concept of how severe the event is that you might find. But it's also important to remember that we should not only be increasing our knowledge over time about the negative aspects of devices, but also the positive aspects.

And so I think to be able to present, over time, the evolving risk/benefit profile is something that's going to be useful in terms of having the context around doing signal detection management.

MR. CAMPION: Good morning. I'm Dan Campion with Quintiles Outcome, with our late-phase and real-world research division. And just to applaud your work, this is a strategic partnership development activity that you're doing.

A couple comments in terms of building the registry infrastructure. One is to help do some forecasting and alerting the field about where those areas of overlap may be, where professional societies

want to be doing quality improvement work or where you think signal generation is needed and postmarket studies are needed, so that before the requirements are put out in terms of premarket approvals or 522s, that there can be an infrastructure in place already, because it's too late once those mandates are out there, to start building the registry.

The second piece on that is where we have quality improvement registries in place already. Moving them up to do a post-approval study is not a trivial matter. Not only as we're talking here, there could be many additional data elements collected, but then you've got patient consents that typically are not collected in a quality improvement registry. That adds a whole other legal layer into it. It also adds an operational level because those sites may be "research naive." They may not participate in trials and things. But the work of getting them to a level where they now need to be able to accomplish a post-approval study is significant.

So we need work to help identify good sites that could participate in a post-approval study and put some resources into helping them do that. Part of the work of building their experience will be the volume. So part of the strategic work is identifying where may there be a volume of post-approval work that's going to happen so that those sites can know they can make investments to become part of a research effort.

MS. RAYNER: Danica.

DR. MARINAC-DABIC: A couple of comments. Maybe first with

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what Dan Campion just said.

One thing that I think is important, that we think about -- we do not think about the post-approval studies always in the context of how we have been asking for them in the past and assume that these are going to be the only way of how one can address the mandated question that FDA imposes at the time of the approval. The nature of the studies, the design of the current studies is dictated by the lack of an integrated, coordinated postmarket surveillance system.

If we had in place the system that we are dreaming about today, and if this is something that is available to all of us, then one can ask ourselves and oneself about do we really -- are we going to need to ask industry to do the post-approval study, de novo studies, that are going to be just designed and implemented and conducted just to address that particular question? Or a lot of information can be drawn from the existing infrastructure and the data sources that we are trying to collect and work together on it.

So in that essence, I would like just us to think about this because much burden of these traditional studies we've heard from Dr. Gross and all of you in this room know very well. And we are very open to looking into better ways to get those questions answered by working together and making sure that there are better strategies to do that.

Then also in response to Dr. Lewallen's comment about these

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levels of transparency or stages of transparency, I think it again speaks to the need for methods and how much time would elapse from when something looks like a signal and by the time you are free to actually call it a signal. And this is why we are here. I think, again, it underscores why, in different clinical areas, there are different advances in terms of how comfortable we are with the data coming from different data sources.

When you mentioned that lots of other registries have utilized the approach that -- you know, discussing among themselves and figuring out, you know, please keep in mind that -- for example, the Scandinavian registries started 20 years ago, in contrast with today's demand of globalization of information and the way of how media sometimes can put things on our agenda, things that are not ready for prime time yet, so we don't have a luxury often to deliberate too long.

I think your comment speaks really for the need for this type of a system, and when something comes up from your registry, at what point do you get others outside of the registry involved? They don't necessarily have to be the entire world, but you know, the system and algorithm, how the system is going to work, other clinicians, professional societies, FDA, CMS, others that can be part of that system.

So I think both of your comments really underscore, from my perspective, those two main issues. Again, going back to the methods and going back to the infrastructure, if we have that, then the shortcut, we're

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going to actually have a much more clear way toward identifying the signal.

MS. RAYNER: Thank you, Danica.

Are there other comments from the floor?

DR. NAFTEL: So if I may, the discussion of signals, I just want to visit that for a second because I don't actually know what we're talking about. So I want to back up.

All of my thinking, when it comes to the signals, revolves around the premarket application. If you go to any of the panel meetings -- let's just go back to the HeartWare panel meeting for an LVAD, left ventricular assist device, and you see all of the discussions about how were the patients selected? Was there bias? How were the endpoints, that is, things going into signals, how were they determined, how were they adjudicated? Are they a function of risk factors? You know, all of those discussions in a well-controlled study, all of those applied to the postmarket and to the identification of signals.

So if you're worried about a device and maybe you only have six-month follow-up in the premarket, but you're wondering if a signal, say, a stroke, after it's gone along at a low hazard, does it have an increased hazard, increased rate? That's a signal I'm interested in, and that's something that a postmarket study or registry could do.

But as I evaluate all of these sources of signals, my thinking is always going back to the premarket, well-controlled study, and what are the

things that that was able to do that a registry can't do? It does have the high level of adjudication, it has to get through an informed consent barrier. You know, I have to think about all of those things and put my thinking of the postmarket stuff within the context of could we figure it out pre? And if we can't, then it's going to be a kind of rough post.

So those are just my rambling thoughts about a very nebulous thing called signal that, to me, we should be saying not signal, we should be saying rates, increased rate of something. Signal, you know, it really doesn't even mean anything to me.

Thank you.

DR. KRUCOFF: So maybe I could follow on that with some thoughts that we could continue on the panel to discuss after lunch, because I do think it's important, if nothing else, that we're really clear when we talk about signals.

Obviously, with breakthrough technologies, we get surprises. So we have to have a system and a way that could tell us that something is happening that nobody ever expected, much less looked for.

On the other hand, the degree to which we can use an ongoing registry infrastructure for efficiency, for prospectively defined questions, I think, is an invaluable tool, as we'll talk about, I think, through the week for the total product life cycle where premarket, underpowered signals, so if the left-handed 80-year-old diabetic women in a particular randomized trial

actually didn't look very good in their outcomes with this new gadget, but it's totally underpowered and it's obviously -- you know, is there a way that we could pay attention to that systematically, prospectively in the postmarket, even to the point of embedding a randomized assignment into a postmarket registry? This is the way I think we have to be thinking in the modern world, and certainly in the United States, to create an efficient, but for innovation, safety kind of environment.

So I think, as we think about signals, there's spontaneous detection, there's retrospective signals that we can sort of search for, if we have gathered the data previously. I think one of the things we could visit -- we've had long conversations with the STAR group and others -- is one of the things we have not incorporated is physician bias in picking a device. So in the real world, when you have four commercially available stents, why do doctors -- why pick one stent versus another? And are they smart or smarter than we think? If we don't capture that in a database, there's no statistical modeling in the world that can help us understand that bias.

So what we're looking for prospectively versus retrospectively, what we're keeping the radar up for are the unexpected that we have never even asked about, and what we do with randomized versus non-randomized data, hopefully these will all be ways of approaching it. And it's not just one signal. There are multiple different kinds of signals that ultimately build the bedside encounter. What are the risks and what are the benefits, short term,

long term, unknowns, of a device that we use?

MS. RAYNER: Are there any more comments from the floor?

(No response.)

MS. RAYNER: With that we will break for lunch. We'll come back at 1:00 and reconvene here with our next panel. We'll see you at 1:00.

(Whereupon, at 12: 00 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

DR. MARINAC-DABIC: We are ready to reconvene.

Good afternoon, I hope you had an enjoyable lunch. And let us now roll up our sleeves and discuss this paper in more detail.

The topic of the first panel that we planned for today is to talk about the national strategy. We have a distinguished group of panelists here that I would like to extend my gratitude for agreeing to serve on this panel to share their unique areas of expertise.

And in particular, let me just extend my special thanks to Anna Slipp, who had no idea she was going to be on this panel, but because our patient representative had a last-minute scheduling conflict and couldn't attend today, I just asked Anna just before lunchtime, and she agreed to be on the panel. We really don't want to proceed without having a patient rep. So thank you so much for doing that.

First of all, I would like to have all the panelists introduce themselves, maybe starting with Greg Daniel. And then after that, we're going to start our discussion.

DR. DANIEL: Hi. I'm Greg Daniel, Managing Director at the Engelberg Center for Health Care Reform at Brookings.

DR. MACK: I'm Mike Mack. I'm a cardiac surgeon, and I am not an outcomes expert by any means. I had the misfortune of being in the

wrong place at the wrong time. I was president of the STS last year when the TVT Registry started, and I got drafted to be the co-chair of that registry, so that's why I'm here.

MR. SECUNDA: Jeff Secunda from AdvaMed. I'm in the Technology and Regulatory Affairs Group. I'm a biomedical engineer by training, and one of my major areas of interest is in postmarket surveillance.

DR. SELBY: And I'm Joe Selby, a family physician, outcomes researcher, and for the last 14 months, the Executive Director of the Patient-Centered Outcomes Research Institute, otherwise known as PCORI.

DR. NORMAND: Hi. I'm Sharon-Lise Normand. I am a Professor of Biostatistics and Healthcare Policy at Harvard Medical School and Harvard School of Public Health. I'm also the vice chair of the Methodology Committee for PCORI and I'm also the co-principal investigator of the MDEpiNet Methodology Center, with co-PI Dr. Fred Resnic.

DR. KRUCOFF: Hi. I'm Mitch Krucoff. I'm a Professor of Medicine and interventional cardiologist at Duke University Medical Center and the Director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute.

DR. SEDRAKYAN: I'm Art Sedrakyan from Weill Cornell Medical College, Associate Professor, and I'm directing the Patient-Centered Comparative Research Program, and also I am the PI for the MDEpiNet Infrastructure Center.



MS. McCOLLISTER-SLIPP: My name is Anna McCollister-Slipp, and I'm cofounder of Galileo Analytics, which is advanced data analytics and visual data mining complex health data. But I'm here today as a patient representative.

I've had Type 1 diabetes for 27 years, and I'm very dependent upon medical devices. And I've been involved in comparative effectiveness, sort of, advocacy policy for quite some time.

DR. MARINAC-DABIC: Thank you.

So we've been discussing, the entire morning, the CDRH's vision for the development of the national postmarket surveillance for medical devices. What we would like to do this afternoon is to try to address some of the specific questions that lay ahead of us once we started thinking about implementation of this system.

So first I would like to pose one question that has to do with your take on are these really the right efforts that we are engaging in, and are there any additional efforts that you see to be vital parts of this national strategy for the postmarket surveillance of medical devices?

MR. SECUNDA: So I'll start, and permit from the alphabet.

I think the efforts are right on. This is very impressive. I said to many people that, in having read the National Strategy, that there were no surprises. This is something that's been in the works for a number of years, various aspects of it, and certainly the need has been around since there have

been medical devices.

I think there's been a lot of progress, even before the National Strategy became a published document, but I would say that the goals, I'm not 100% sure that the goals are clear and complete. I get a little concerned when the goals are so broad that they lose meaning. So that's something that I would be looking to hear in the discussion, as to whether the goals are specific enough, whether we're trying to be too broad in our effort, and as it's been said in the morning, trying to be all things to all people and accomplishing less than we want to because of that.

DR. MACK: So I would make two comments. I think that the strategy is right, and I think that the overarching goal should be twofold.

One is more robust postmarket surveillance because I think everybody agrees that it's not sufficient right now. We don't have a true numerator and a true denominator of the incidence, and before we get involved in discussing what signal is important or not, I think that we need more accurate information than we have right now, and hence, a more robust postmarket surveillance system, which this vision outlines, is critical.

The second part is what Jeff mentioned this morning about moving the needle between pre-IDE and postmarket surveillance. As everybody is aware, innovation is being driven overseas; a lot of medical device companies, their strategic plan is to never come to the United States now despite the fact that it's still 50% of the market because the regulatory

pathway and expense is so burdensome.

And if we can have a robust postmarket surveillance system that perhaps makes the pre-IDE pathway less burdensome from the regulatory standpoint, then I think we have accomplished something in terms of not having innovation leave the United States or never come to the United States, but look at the United States as a more friendly environment for the introduction of new technology.

DR. MARINAC-DABIC: Greg.

DR. DANIEL: Yes. I think I would agree that these are the right efforts, and these are the right goals. So if I think about what that vision is, the development of a national infrastructure for evidence development using routinely collected healthcare data, it is the right vision, it's critical for devices.

I've got a couple comments related to how can we move this forward. What strikes me is that this vision is very important, but it's also a vision that could be usable by other federal agencies. For example, such a development of infrastructure is necessary for Sentinel to move on.

Primarily, you'll hear later that Sentinel right now is largely claims data, but to move that forward, getting claims data integrated with clinical data, with electronic medical record data, with registries, with patient-reported data is essential. And also for drugs that are innovative and go through more expedited review process, the availability of an

infrastructure that is using routinely collected data could be efficiently leveraged to confirm benefit and further evaluate risks and safety profiles of drugs that go through expedited review process. So even within FDA, such an infrastructure would be very useful and important for CDER and CBER, as well as CDRH.

Outside of FDA, I think enabling an infrastructure that can produce an opportunity to maximize the use or more efficiently use things like coverage with evidence development within CED to enable patients to have access to innovative products where there might not be enough information to make those decisions, having an infrastructure like this could really move that forward.

I won't steal from Joe, but I suspect that doing research with patient-centered outcomes research as well as comparative effectiveness, having an infrastructure could be very useful for that. So my point is that the catalyst for moving all of this forward could happen if FDA and CMS and PCORI and VA and other federal-level agencies can collaborate.

The second point is that to move this forward, that the data are largely owned by private organizations: payers, hospital systems, providers, as well as patients themselves, and academic medical centers. So an important aspect of moving this forward is to get those stakeholders at the table early, involve them in the strategy to move forward and involve them in the governance structure. I think that that will be very critical to identify that

everybody coming to the table will have a different business case and will be coming from different interest areas, and identifying those, articulating value for each of the stakeholders would be very important to move forward.

The third comment that I have is that -- and I heard this this morning -- we have to recognize that electronic healthcare data are continually evolving as health reform moves forward; as we move towards more accountable care organizations, patient-centered medical homes, what the electronic data are, how they're used, how they're stored, and how they're retrieved will continually evolve over time, and so, therefore, the methods that we have to use those data for evidence generation will have to evolve over time. We need to understand what those data are telling us and how to appropriately use those. So I did see that within the strategy. I think it's important to focus on continued methods development.

And then, finally, with regard to the unique device identifier, very critical. It's very important to have that into the electronic infrastructure so that we can track performance of devices over time. But it's important to note that the UDI, itself, is not useful unless there is full implementation from all of the stakeholders and that we use UDI, that payers, providers, hospital systems implement UDI into the electronic infrastructure.

DR. SELBY: Thanks.

Well, actually, you did steal some from me, Greg, and I'm going to therefore reinforce it, but start by just saying that the notion that the

existence of these islands of rich, electronically-stored clinical data around the country that could just be linked to allow safety research compared to effectiveness research and maybe even facilitate large clinical trials is not a new idea, and it's not a profound idea; it's more in the order of a no-brainer.

It's been tried by a number of people in a lot of areas, more in safety, I think, and drug safety, but for a lot of other purposes including outcomes research, and despite the beauty of the idea from the point of view of a research funder or from the point of view of researchers, hasn't really taken off.

And so now we see people retrenching from investments they've made, and it begs this question of how are we going to get the various players, including, as Greg said, the health systems who own a lot of the data and -- with my hat on, Patient-Centered Outcomes Research Institute -- patients to really participate.

I was not here this morning; I did the read the materials that I think described what was talked about this morning, and I was struck by the absence of much mention of patient-reported outcomes. And maybe I did miss that, but I would think that in devices as in drugs, and compared to effectiveness research, patient-reported outcomes are among very important outcomes; certainly from the perspective of patients, they are.

So as Greg said, what's the business case for each party? And we know that the business case for the FDA or for the NIH or for AHRQ -- we

know the business case for researchers who would like to build these data resources and then administer them and conduct research in them. We haven't really demonstrated the business case for the systems that have to do everything from implement the UDI to make the data available, to work on the quality of it and to straighten those kind of reports, and we haven't made the business case for patients yet.

And so I would really challenge us to think about how, in fact, we make this an interesting enterprise from the perspective of patients and from the perspective of systems from Day 1. Patients need to sense that this is a resource that they can use to address questions, perhaps to build patient communities of people who have had similar devices implanted.

Systems need to be able to compare their outcomes or their utilization patterns to that in other systems in ways that predict proprietary interests but provide value.

In the process, I'd say a couple last things in closing. One is that for patients to really be fully engaged in a process like this, it takes typically some training to get patients kind of comfortable dealing with academics and researchers, as we talk about the intricacies of studies. It also takes some training of researchers to be able to appreciate the patient's perspective. And in that, in that training of patients, researchers, and other stakeholders, in doing a patient-centered version of safety or effectiveness research, and also in terms of developing methods specifically for examining

the safety or the comparative safety or the comparative effectiveness of devices, that's a methodologic area; both of those areas are.

Training researchers to participate, training patients to participate, and developing the methods for this kind of research is an area that PCORI has stated interest in. So I hope that we can be a partner with you. I think that it's going to take partnership. These things are just too expensive if we don't have everybody actively engaged and enthusiastic about it.

DR. MARINAC-DABIC: So can I just ask one follow-up question? What, specifically, PCORI can do to contribute or to work with us from the very beginning?

DR. SELBY: Well, first, thank you for inviting us to be here today. We had a meeting, not unlike this meeting, in Palo Alto in early July, and everybody showed up kind of obsessed with this notion that I mentioned of all this data that just, if it could just be linked together, we could examine the quality of the data and ultimately improve the quality and the consistency in formulating the data cross-systems that we can really begin to do a lot comparative effectiveness research.

We came out of it with just that appreciation that I mentioned as needing to make the business case to the key players that have to be engaged if this thing is going to happen, if it's going to be at all affordable.

I think PCORI continues to have interest in contributing to a



national infrastructure; it knows it can't do it by itself, suspects that no other entity can do it by itself, either, so we'd be glad to be a party to discussions like that.

And then I did point to those two areas where PCORI would be particularly interested, I think, which is bringing patients along and equipping them to participate actively. And the second one is contributing to the analytic methods.

DR. MARINAC-DABIC: All right. So the reason I'm asking is we're going to embark this afternoon on initiation of the discussion on how we envision the system, how we envision the governance of the system, how we envision the roles of each party within the system.

I really think the point that you had raised with regard to making a business case, why this is important for patient agenda, and not only stimulating the patients' participation in research and training for that research but also patient perspective at this stage as we're trying to develop the system and as we are developing the priorities, as we're developing the governance of it and the roles of patients in the future, bodies that will govern this type of surveillance system.

I think this is one of the things that, I think, would be a really great implementation point. And I'm going to write this down, to contact you after this about the business case.

All right, so Sharon-Lise.

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DR. NORMAND: So let me first start with my PCORI hat, to say that certainly PCORI, the Methodology Committee, has a lot of interest in developing both analytical strategies to analyze all these data sources, which I think, somehow, even if we had perfect data, people think okay, we'll just analyze it. Well, it's just not that easy, simple, or correct.

And then I also, to emphasize, I think that the Methodology Committee is also leading the way in terms of patient-centeredness, in terms of getting and teaching patients and researchers to interact. So I'm reemphasizing things that Joe said but, I think, from the Methodology Committee standpoint, that it's fair to say that we're very, very interested in that, and so it's something we would like to partner with.

Now, let me take that hat off and talk about my role -- think of me as, sort of, a statistician, which I am. So I think the efforts and the goals are correct. However, as Danica told me in another public meeting, "Don't be nice, be yourself," I have the following comment or question.

So we've been talking about -- and I think Dr. Naftel brought this up in an indirect way earlier today, and that is the following: There are premarket approval studies that are done. Then we get to the postmarket study. And I think we need to understand, and let me just say it this way, I need to understand better what the questions are that we're answering from a post-approval study or the premarket setting. Now, I'm saying that I know some of them, but I'm also saying it because I think there's this sense that

we're answering the same question and we're not; at least in my opinion, we're not.

In the premarket setting, the question is the "let me talk about the experimental effectiveness" in sort of this ideal setting and looking at the device effectiveness. And when I say that, I'm talking about, sort of, effectiveness in terms of efficacy. I'm pretty sure, in the post-market setting, we're looking at something different.

And so I raise that issue because I do think that has implications for how good the data are, that has implications for the types of questions that we ask, and I also think it impacts what type of errors or error rates we're willing to make.

And so I always get to Ted. I say something, Ted disagrees with me. I'm going to disagree with Ted because he's sitting down now, so he can't speak right now. But in any event, sort of, these issues in terms of how you balance these things.

I would submit, and it would be good just to -- I know that's part of this. But I think the post-approval studies in a postmarket setting ask a different set of questions, and I just think we have to underline that, at least in my mind, because we're going to get stuck because by the way, you're going to have to randomize to do most of the questions that we're -- so that's the issue, and so I just want to not lose sight of the fact that are they right efforts, yes, but I just want to make sure that we all understand what we're

trying to estimate, what we're trying to infer, what we're trying to learn.

DR. MARINAC-DABIC: Okay. One follow-up question.

All right, you did focus your comment on one particular tool within the overall postmarket strategy, which is the mandated post-approval studies. And I think a part of the puzzle and the challenge is really for us at the FDA also to think about are we asking the right questions and why there is no better participation in our mandated post-approval studies.

So I think a part of the overall strategy is that we examine what are we actually asking some of them in questions or can some of our questions be answered through different means. And I think that's also part of, should be part of, the discussion.

I want also to ask you what is, in your opinion, the role of academia in moving this forward? Because you're wearing several hats here obviously, and I'm now going to ask you, by wearing your Harvard hat and Methodology Center hat, how do you see what specifically academia can do to actually advance this and what is the role of academia?

DR. NORMAND: And this is completely self-serving, as an academic, but I think academia has a large role to play in terms of generating new methodology and that can be done by graduate students, post-doctoral students, funding mechanisms, of course, that's what we're thinking about. I'm just being very brutally honest.

But academia is quite interested from, let's say, the statistical

standpoint, not necessarily the clinical standpoint; the statistical standpoint, the epidemiological standpoint, is that we have, in many institutions, all institutions, some very, very bright people, bright, young people coming through. And I think having them get excited and engaged in terms of accessing and thinking about efficient and novel ways of answering questions and utilizing and developing data, so we often focus on analysis, but there's the design aspects, having some people think about, if I want to think about designing -- I think Dr. Krucoff had mentioned several times, you could have a database in which you can nest the study, a prospective study.

So I think academia is quite interested in research, but also in the teaching. I think, my sense is -- I think we heard this earlier this morning, and that is misinterpretation of findings. I actually profile all the hospitals in Massachusetts for cardiac care, and you can imagine trying to explain what some of those statistics are, and so I think there's this strong educational component that academia could also provide to -- I'm not trying to sound all-knowing, but to industry and to patients and also to the FDA and vice versa.

So I think we're also very eager to help with not only developing but disseminating and teaching to say here's how you interpret something; here's wrong, here's what's right.

DR. MARINAC-DABIC: And how much can be done, really, to examine what type of programs we have in academia, within academia, that will bring the medical device, epidemiology, and biostatistics, and with

application in medical devices to the young and bright students from the very beginning so that -- we recently looked, for example, at a survey at International Society of Pharmacoepidemiology and found out that there are only 21 graduate programs in the United States in pharmacoepidemiology. So we are now contacting all of them to figure out what can be done to add medical device epidemiology to their program.

So these are that thinking that we have on our end, but I'm very happy to hear, and something I know that many, many of MDEpiNet sites and other academicians in this country are very interested in actually working with us to advance this. So I'm now looking for some of the actionable items that if we can commit that each of us are going to move forward, is this something that you think you can help with?

DR. NORMAND: Yes. And then I'll make a final point. And that is I was afforded the opportunity to do sabbatical at the FDA, in the Division of Epidemiology, and that formed also an exchange of letting people understand opportunities. I think that's an important one, too, so absolutely.

DR. MARINAC-DABIC: All right.

DR. KRUCOFF: I think a lot of these comments are actually synergistic with one another, and it's not a coincidence, because I think what the white paper helps do is crystallize that as you address an ecosystem -- and innovation, device innovation, really is an ecosystem -- that we, on the one hand, have to understand all the details, of which there are many

different sorts and kinds, but also the contexts in which those details are integrated, analyzed, or to provide any kind of conclusion.

So how do you get started along those lines? I think one way is to recognize, first and foremost, as we were saying this morning, that at any given level, the quality of the data, what's collected, how it's collected, how it's analyzed, whether it's being used for retrospective hypothesis generation or unexpected signal detection or in a prospective randomized trial premarket approval construct, that those are all going to be different; whether it's used for a breakthrough technology or a mature technology, space is going to be different.

And at the end of the day, what's painted in the white paper, to me, the only real criticism I have for what it is, is that it describes itself as postmarket surveillance, and we are in an ecosystem that's more than just postmarket surveillance. So it's all the right stuff, but we've got to be able to both step back and see that if this moves the bar, maybe the first place we need to start is where all the stakeholders really have something that matters to all of us that's the same, where is the core common ground?

And here, I think, how safe is safe enough, how fast is fast enough, how fast can I get this technology to the bedside with reasonable assurance of safety. We need to revisit what do we mean by reasonable assurance. And I think, as Mike said, Jeff pointed out this morning, if that means that we actually, by creating a strong postmarket national information

system, can evaluate a device that may save lives and in the premarket be comfortable enough that if we don't know if it really saves lives in all the left-handed, diabetic, 80-year-old women because that group is underpowered, that we will, when we get into the postmarket, so we don't have to wait five years to collect enough 80-year-old, left-handed women before the device is approved.

If what is reasonable assurance actually helps us bring safe and effective devices to the bedside earlier because we're responsible about collecting, contextualizing, and analyzing data once it's in the market, in the real practice of medicine, then there's a huge value equation there for the industry that makes these things, because you're going to get to market three or four years earlier. In some markets, that's hundreds of millions of dollars.

This is an ecosystem, and I think at each step of the way, what the quality of the data is, if we're looking for a 0.6% per year annual linear hazard and we have really noisy, messy data, then we're never going to be able to detect that. So everything matters, but different things matter differently to different stakeholders; different things matter differently to pin down the question you're trying to answer.

Within all of this, though, a central river of high-quality information that comes from clinical sites nationally on a routine basis using uniform definitions would put us in a much stronger position for each stakeholder or for each question to be addressed better than it is today.



So I think the document lays out some very good starting points, but we have to look higher. This is not just, in my opinion, about postmarket surveillance; it's about the total product life cycle. It's about mature devices as well as breakthrough technologies. But it's different for each of those.

And at the same time, I think, nationally -- you know, what can a doctor tell a patient in an informed consent discussion about a valve that will halve their mortality if they get it now in this first year compared to not putting the valve in but honestly say, well, we have no idea how this thing will behave in three years or five years but we will, because your data and your follow-up is going to help us track that over time. As a physician, that's something we don't have today. And we fill those gaps in with a lot of other talk. So better to fill it in with knowledge than with talk.

So I think we have to respect that we need context. We have a ferocious number of details that we can bring to bear, brilliant ways to analyze data. We've got to know what the questions are. And we're going to have to create a conversation or convene some sort of -- it's not going to be just the four days this week. This is a beginning, or maybe honestly you could say this is a middle. This is definitely not an end. Dynamics of medical device technologies are very fast. So there's got to be an ongoing process that also helps tune all of these agendas to stakeholders over time.

DR. MARINAC-DABIC: So wonderful question, Mitch. How do

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you envision the governance of this national system? How do you envision the body of some kind that will start implementing this vision and working together, from the very beginning, to fine tune this document, make it really a document that will be embraced by the diverse body of stakeholders? So that's one question that I have for you.

DR. KRUCOFF: I'm not so sure -- you know, Danica, I'm a great fan of public-private partnerships. I think they provide transparent environments. I think there are a number of examples where you can foster a real pre-competitive focus, what's the ground that's a problem for all of us. And then suddenly you're combining everybody's experience and expertise rather than silo-ing individual groups.

I think to have that sort of public-private partnership environment can then assign transparently, in the same way a federal agency can transparently assign, key deliverables that are put on timelines and put into responsible hands to coordinate, but not own, every part of a process. So orchestration of something that manages an ecosystem is really trying to grab the synergies. Who's got the strength to actually get this piece together and stay in touch with all the other pieces?

A public-private partnership can foster the communication between all of the pieces. But, ultimately, there has got to be an ability to assign to specific expertise deliverables for analytic models or for information management or other, sort of, critical parts.

DR. MARINAC-DABIC: All right. Art?

DR. SEDRAKYAN: Sure. I really like how FDA framed the message in the document. It really has both short-term and long-term vision. And yes, the devil is in the detail, but this is really critical vision, and it's a clear -- in my head, it's a clear document. It just shows us where the path is and how we need to collaborate and how FDA is offering this to the scientific and clinical community and policy community as a vision how to move forward.

We have a very complex healthcare system in our country. It's not easy to build that infrastructure that's a European, sort of, worldwide as possible to build because of the efficiencies that are possible to achieve in a single payer environment compared to multi-payer complex environment, often fee-for-service. We really need to incentivize a lot of parties to be part of that national vision. So I think it's an enormous task, and it's not possible to achieve by FDA alone.

I am currently on the MEDCAC, and I'm going to be vice chair for MEDCAC, a Medicare advisory committee for coverage, and we're facing a lot of the same questions. CMS, particularly in terms of coverage determinations, is facing the same device questions often. In eight or nine out of 10 questions would be what the evidence is in the real world, is this technology working, and what are the subpopulations of patients that are benefiting from this technology, exactly the questions that FDA wants to

know.

Coverage with evidence development that CMS is working on in a new policy that is coming up from CMS, it can tremendously help to build a national infrastructure, help build registries, is a wonderful tool to collaborate because right now, it's a very narrow vision of what that tool is and how it needs to be utilized, and yet, we know -- an example, again, TVT Registry, a number of other registries, that payer has an important role to play in helping to build that national data systems and infrastructure.

So, again, we really need this view, the data systems and evaluations that go with it as it continues effort, ongoing, and we have to learn to act on this evidence. I don't believe it has to be hypothesis-driven data collection. I think any national data system that continuously evaluates the care has benefits of its own. So it has capacity to improve the care as it's being delivered, and we can build from that. It doesn't have to have a lot of questions in mind to make it so complex that we can't achieve it. We need to really have that efficiency in mind in thinking about this so again, the devil is in the detail, that it doesn't suddenly become a task that nobody can achieve.

So I think those are critical thoughts in my head. And I certainly believe academia has an important role to play. A lot goes into thinking about grants, writing in academia, work with the hospital and work with the clinicians to think about how we need to build that EMR-based research entity or a database or a registry. It's not happening in many hospitals, and

there's some real enthusiasm, a few good clinician/scientists that are driving at this time. This is not incentivized in any way by the current system we have for grooming that next generation of scientists in academia.

So I think that fellowship concept meets a certainly very helpful -- again, having that on the agenda for a lot of public health departments. In fact, I will argue clinical departments need to be very much interested in this rather than, often, public health departments because they're the ones who understand a lot of the details and thinking that they're part of a big community that needs to evaluate the care as it's provided. It is certainly also important for future sustainability.

We can't fund a lot of this data collection. It needs to be also enthusiasm of clinicians who are part of this effort, to feel that this is part of something big. And really need to make sure that our nation is leading this effort worldwide rather than catching up, at this point, for many things other than some professional society-driven efforts, again, which are, I have to say, wonderful but voluntary reporting systems, we're trailing behind many other countries.

DR. MARINAC-DABIC: All right. Thank you, Art.

And Anna, do you want to --

DR. KRUCOFF: Can I make one --

DR. MARINAC-DABIC: Sure.

DR. KRUCOFF: -- real quick observation just because Art stirred

this?

When we talk about academia, I think it's important that we remember that another side of academia are our professional societies, and we are investing hugely in our professional societies on gathering data for best practice, for guidelines that are reviewed by independent processes that currently are entirely divorced from regulatory processes. Isn't that silly?

So another place, I think, that academia and federal agencies could conjoin is shouldn't we be paying for our best practices? I mean, this in theory, I guess, is what comparative effectiveness is. But when we talk about academics, it's not just Ph.D.s, it's M.D.s and professional societies who have a lot of resources already in place and a lot of engines generating postmarket registry data to guide our best practice. We could leverage that.

MS. MCCOLLISTER-SLIPP: As a patient, I'm listening to this, and I am incredibly encouraged that the Agency is taking this on, and I certainly am happy that I'm not in your role, Danica, trying to pull all of these stakeholders together and thinking about this from so many different perspectives.

But I mean, again, my area is Type 1 diabetes. I have three medical devices on me at all times: an insulin pump; a glucose meter, a continuous glucose meter; and a blood glucose meter. I interact with them on a regular basis. It's sort of a combination of medical device and consumer electronic interaction that I and other people with Type 1 diabetes have. And

I think, because of that, there is a lot that people within the diabetes community especially can do to help this process and I would say I encourage you not just to have people like me and others involved in designing infrastructure in the system for moving forward, but thinking very innovatively about how you can create an atmosphere for, sort of, the consumerization of medical devices.

As a patient who lives in Washington, D.C., I'm often very frustrated by the tenor of the discussion about engaging patients. Now, that tends to be just putting up a website or providing information. I think it's much more helpful and much more productive if you can involve patients in the process of data collection, data curation, creation of systems for -- you know. I mean, look at iTunes, look at the mobile health applications on iTunes. People rate them all the time. You can see which ones work better, you can see which ones work worse.

Now, that's going to work better for some devices than others, but there is a lot of really good information out there. Patients are smarter than I think they're given credit for, and they're much more interested than I think they're often given credit for in these types of discussions.

So I mean, one, to the extent in which you can give us power, responsibility for participating in this process, I think if the Agency can sort of create a mechanism for that to happen, it would be really helpful. I really liked the recommendation about some sort of mobile app for adverse event

reporting.

I guess I would expand that a little bit to say not just adverse event reporting, but device malfunctioning reporting. I don't know how the Agency determines which is what, but you can have multiple device malfunctions, but it doesn't necessarily impact your disease, but it does impact your ability to control it on a long-term basis.

So to the extent of which that kind of activity and that sort of a framework with thinking about including and giving patients responsibility for this process can be integrated into the system, I think it would be really very helpful and in some respects simplify the process.

DR. MARINAC-DABIC: All right. So I would like us now to build on -- comment about public-private partnership and expand an idea of how this organizational structure might look like because those are two remaining items that I'd like to discuss with this panel so that we leave this session with an idea what the next step is and achieving that particular vision for the governance, and also discuss some timelines in which this can be achieved.

We certainly do not want to put something off within the next year or two or three or five. We feel, at the FDA, that things need to move on much sooner than that, and by the end of this year, we certainly would like to have the draft of the implementation document and some clear idea of what the next steps are going to be in terms of the governance.

DR. KRUCOFF: I can at least start from both good experience

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and scars, so -- and as a public-private partnership ultimately involves volunteered time by people who have other day jobs, that sometimes is a good place to start, is just by outlining a mission, and I think you've pretty much already done that, and then seeing, from volunteers, to actually create a charter, formalize the mission, a charter that creates an organizational structure. This is all, sort of, the dull, boring, but critical stuff to going into a transparent public-private partnership.

And then understanding, if there are financial resources necessary, where they're going to come from and see who volunteers to actually make that happen. And out of those who volunteer, about half of them will actually make that happen. So that's one place to start. It's a pretty level playing field, and it ultimately comes down to who's really driven to help put this together to get it going. The first step is, for a PPP is, to get it going. And I think the workload there is just put it out there and see who volunteers.

MR. SECUNDA: Yeah, I'm still a little concerned about the solution to every problem and each of the different stakeholders -- and I'm talking more on the FDA, CMS, perhaps professional societies. They all have different perspectives; they have different needs, all of which are valid. But I think we have to be very careful not to become bound up in satisfying all these different needs. We need to have a real focus.

Other organizations can benefit from that, from

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standardization of a number of different things, whether it be methods of governance all the way down to the types of data that are routinely collected in all cases. But I think we really do have to have a clear focus that benefits the patient, and I'm thinking more in terms of the device aspect of that. Not to say that the patient outcome, that the provider information isn't absolutely important, but we are sitting here with the FDA, and I think that should be the dominant focus and not spread ourselves thin to the point where we can't accomplish what we all really want to do.

DR. NORMAND: Can you help me -- I just -- clarification. What do you mean by -- so the patient outcomes have to matter. What did you mean "just by the device?" You made that comment. I don't understand it.

MR. SECUNDA: Adverse events, performance of the device.

DR. NORMAND: Okay. So I would disagree with you. I think we need the patient outcomes, as well. I just --

MR. SECUNDA: I'm not saying that -- of course, we need the patient outcomes, but I just want to avoid where you have too many people in the room --

DR. NORMAND: I understand, yeah.

MR. SECUNDA: -- for that setting up the governance, and everyone has their issue, and we don't accomplish what we all want to do.

DR. NORMAND: So I think there's an issue with -- I think I would state that we've gotten, the royal "we," have gotten a little further

away from patient-centered outcomes, and I think it would be important to put those back on the agenda. So that's one thing I would say.

DR. KRUCOFF: You know, I think rather than thinking this is sitting down with the FDA, I think we'd be all very smart to realize that what we're sitting down here with is the public health. And the FDA has a major role in that, but so does CMS, and so do how we understand it's the public health, and medical devices play a role in that, but it's a complex role.

And I think, from that point of view, that's where a public-private partnership -- you know, ultimately, whether it's an instrument manufacturer who makes a wonderful profit by making the public health better by creating better devices and selling them or whether it's the government being cost-efficient and deciding what kind of technology should be reimbursed or not.

Ultimately, the starting point, whether it's a physician at the bedside or whether it's a patient or a patient's child wondering about should we do this for my mother, there is a common ground here, and it is the public health. And it was said earlier this morning, sooner or later, no matter what profession we're sitting in, we're the patient or somebody in our family is the patient and we live in -- at least most of us, I think, live in the United States of America.

So if we start with the public health part, then a public-private partnership environment can start to drill down on, "And what are the key

details relative to how we do it today and where we can move forward?" So I think rather than sitting with the FDA, if we're sitting down with the public health in mind, that then we can get our arms around this.

DR. MARINAC-DABIC: Art.

DR. SEDRAKYAN: Quick comment about that. I think a step-by-step approach to public-private partnership is certainly important, and I argue that the device evaluation, particularly safety and effectiveness and patient experience with it is really a neutral topic that a lot of clinicians and patients and policy makers can embrace. It's not about comparing if technology does better than usual practice, the systems that we're talking about in the first step of creating evaluation of these products.

Device evaluation can be part of interventional care. A spine surgeon might not want to get into whether I should do spine surgery or not, but they would like to know if the cage works, if there are different cages that are better than others. So it helps to lay the foundations, what we want to achieve. It's about safety of the product, at the end of the day. We can later on link if a clinician has anything to do with it or not, but a first step, I think, is good to link to device safety.

DR. MARINAC-DABIC: Let's go back to Jeff's comment about the FDA. What do you think the role of FDA is and should be in this type of public-private partnership? All of you.

MR. SECUNDA: Well, FDA is responsible for regulating the

device industry, and through that regulation, to enhance, promote the public health. But that's my perspective. I just want to make it clear, should be clear, that the public health, of course, is the bottom line. This is what we're all here for. I'm trying to be perhaps a little more practical in getting it done more efficiently and therefore focusing on the device aspect.

DR. MARINAC-DABIC: Any other thoughts about this-- let's imagine in six months we are going to convene or put together the governance body that will have maybe 15 members, and let's just assume that there are going to be some representatives from FDA, from AHRQ, from CMS, from NIH, from integrated healthcare delivery systems, from patient organizations, from other entities that are all under the system. So how do you envision the role of FDA be in this type of environment?

MS. MCCOLLISTER-SLIPP: I would think that it would be -- I mean, I certainly don't want to speak on behalf of industry, I'm a patient, but I would think that -- I mean, if you look at the Institute for Healthcare Improvement and some of the issues that Don Berwick dealt with when he was first getting started.

I mean, one of the biggest issues was transparency because people were afraid to share data about mistakes because they didn't -- I mean, they didn't want their competitors to get a hold of it, they didn't want the trial lawyers to get a hold of it. You know, they were concerned about all of these things, and because of that, we kept repeating mistakes over and

over again, and people kept dying in hospitals unnecessarily because of hospital errors.

I mean, maybe the FDA, as a government agency and the convener of this public-private partnership, could -- I don't know what the mechanism would be, perhaps create a non-punitive sort of environment in which manufacturers are encouraged to share the kind of data that we all know that they collect, such as what I referenced this morning, in terms of all of the cloud-based data, syncing in data storage that the insulin pump manufacturers have.

That data is there. It's really rich. It's got lots of good stuff in it. But I would hate to be in a meeting with the legal people at Medtronic or J&J or whomever when you talk about trying to release that. But, I mean, one thing the Agency does have is the ability to make it so that this isn't something that the manufacturers have to fear but perhaps create a system of incentivizing them or promoting -- you know, giving them the ability to share this kind of data in a much more free way without the fear of the regulatory hammer coming down.

DR. KRUCOFF: So I would toss the FDA's words right back to you, Danica, that the first foot in the game for the Agency, in my view, is not the police role; it's the scientific partner role. I mean, the FDA has the largest body of best-informed people and experience that's relevant to this whole medical devices universe of any single stakeholder.

So that, to me, is the critical first part, and then the fact that they're in a position to actually influence the regulatory product life cycle machinery so we could make more efficient -- we could take advantage of leverage-able, more efficient ways of collecting data or registries -- that's a double plus -- as opposed to entering as the police where we're going to raise people's concerns of, gee, I don't want to be honest here because they'll arrest me.

So I think the Agency needs to continue its -- these are Agency words, but it is very important that we get to the point where the Agency is a scientific partner in the innovation ecosystem, and I think this kind of environment and a public-private partnership is a perfect opportunity for that side of the Agency to step forward.

DR. MARINAC-DABIC: Any other thoughts?

(No response.)

DR. MARINAC-DABIC: I clearly agree, and I very much like the concept of TPLC approach. And I think, as a theme, maybe it's not in a title, but the entire context of the document really focuses on the total product life cycle evaluation, and examples that we provide talk about moving to premarket space and the methods development goes beyond just surveillance methods. It's really how you evaluate, how you generate evidence, how you appraise the evidence and make scientific decisions based on that evidence.

So I like very much that comment, Mitch, and I think it's good that we think in that perspective. The public health perspective, also very important.

One thing that I would agree with Jeff Secunda is that because devices -- and the entire methodology around assessing performance of medical devices and clinical outcomes associated with medical devices and the data sources and the lack of UDI, all sorts of things that makes us decades behind the pharmacoepidemiology world necessitate some extra push, some extra attention, and making this under the overall umbrella of public health and within our healthcare system and with global implications, certainly. But it does require focus on what are those unmet needs in the area of devices research, devices evaluation in both pre and postmarket.

So, again, one question that I have, and we need to move on to the next panel, is if you are called upon by us to volunteer your time to make this happen in any capacity, as we put together the charter and put together all the thoughts behind how to implement this, would you do that?

UNIDENTIFIED SPEAKER: Raise the hand.

DR. SEDRAKYAN: Absolutely.

DR. MARINAC-DABIC: Is anybody on this panel who wouldn't do this?

(No response.)

DR. MARINAC-DABIC: All right. So --



DR. KRUCOFF: In addition to your day job.

DR. MARINAC-DABIC: In addition to yes. So I would --

DR. MACK: The TVT Registry has become my day job, unpaid.

(Laughter.)

DR. MARINAC-DABIC: I would like to very much thank you for your participation today for wonderful ideas. I wrote down every single one of them. I will be in touch with you after these meetings to fine-tune some of these ideas and talk about the next steps in the context of what we are going to hear throughout the next four days.

And now I would like to invite Dr. Gross to convene his panel that's going to focus on active surveillance. Thank you.

(Applause.)

DR. GROSS: Okay, good afternoon. I think we'll start Panel II. This is the more straightforward panel, so we'll have lots of solutions by the end of the panel discussion.

We're to focus on Active Postmarket Risk Identification. And there's a slide I have up on the projection screen, which is very relevant to this discussion. The FDA Safety and Innovation Act, Section 615, which is a new provision, asks CDRH to do active postmarket risk identification and analysis. And it refers to a provision in the Food and Drug Administration Amendments Act, Section 905, which asks our drug colleagues to do the same. And that effort has become known as the Sentinel Initiative. The

Safety and Innovation Act also asks us to expand the postmarket risk identification system to apply to devices, so to expand Sentinel to include devices.

Before we begin the discussion, I'd like for each of the panelists to introduce themselves, starting with Eric Peterson.

DR. PETERSON: You've got it done. Eric Peterson, Director of the Duke Clinical Research Institute.

DR. RUMSFELD: Hi, good afternoon. John Rumsfeld. I'm the National Director of Cardiology for the Veterans Health Administration.

DR. RESNIC: Hi. Fred Resnic. I'm the Chairman of Cardiovascular Medicine at Lahey Clinic and co-principal investigator of the MDEpiNet Methodology Center along with Dr. Normand, and an interventional cardiologist.

DR. KUNTZ: I'm Rick Kuntz. I'm a cardiologist and a Chief Scientific Officer for Medtronic and a member of the Board of Governors for PCORI.

DR. STEINBUCH: Good afternoon. Michael Steinbuch. I'm with Johnson & Johnson Medical Device and Diagnostic Segment, and I'm an epidemiologist in the Safety and Surveillance Center of Excellence.

DR. ARCHDEACON: Hi. I'm Patrick Archdeacon. I'm a Medical Officer in the Office of Medical Policy in CDER, and I'm the clinical lead for the Sentinel work that's being done within that office.

DR. GROSS: Okay, great. I thought I would start off by asking Dr. Archdeacon, before you leave --

(Laughter.)

DR. GROSS: Okay, go ahead.

DR. ARCHDEACON: No, I'm fine.

DR. GROSS: Okay. So I mentioned that the call for active postmarket risk identification was launched in 2007; it's become known as the Sentinel Initiative. And so how has Sentinel approached active postmarket risk identification? Sort of give us a high-level view of that.

DR. ARCHDEACON: Yeah, thanks. So, fortunately, that was the question I anticipated I would get.

So I guess, first of all, thanks very much for including CDER here today. I'm very excited to be here, and I think that will circle back to some of the comments that I have.

And I guess the first thing I'll start by saying is to remember that -- I guess my understanding of the Sentinel system is that it's sort of really an aspirational goal still, and that a lot of work is being done towards that, and how that works is considered part of the Sentinel Initiative. So I think some of the work that we're talking about here today, to me, seems like it could be described as Sentinel. But I think what you're asking me to talk about is the work that's being done elsewhere within FDA that we also consider part of Sentinel. And there is quite a bit of it, so some of those

things are strictly within FDA, some not so much.

So OMOP, for instance, is I think part of Sentinel, but it's industry-wide. I guess the ones that I'll focus on really are the many Sentinel projects that largely reside within CDER and CBER at this point. And, specifically, I'll talk a little bit about some of the background with PRISM, which is some of the work that CBER did as part of Sentinel that's now starting to get folded into the Mini-Sentinel project.

So PRISM is the Post-Licensure Rapid Immunization Safety Monitoring system, and a lot of the work initially done by that group is looking at vaccine safety, and so obviously, that falls within the purview of CBER. And I think the reason I bring that up is certainly it's related to the work that we were doing within CDER, but a little bit different. I think it was great that CBER took the initiative to develop the stuff that was of interest to them while we were doing work in areas that were more relevant to us, and now we're sort of seeing an opportunity to fold those two together. And so maybe that's a little bit of a model for what we could be looking at here.

I think we're very sensitive to the fact that devices have a different set of problems than we're seeing with biologics, and we're seeing with drugs in that it's very reasonable that you guys are developing different tools to approach it. The same time, I think, we see in the future an opportunity where we'll eventually want to pull these together. So we're working on the same puzzle from sort of different sides.

I think one thing to keep in mind is where that metaphor sort of breaks down is, you know, if you really have one puzzle, it's inevitable that the puzzle is going to come together. It's a little bit different here in that if we're building some infrastructure, it's really important for us to be having communication all along the way because it's not inevitable that the puzzle will come together.

So I think that one thing we're very lucky with PRISM and Mini-Sentinel, you know, we had some of the same people were involved in both of those projects. So Harvard Pilgrim was part of both of those. But different people on different floors of the same building, and so it wasn't a total slam dunk to come together, but with a little forethought it was pretty easy to do. Again, here a lot of the same people but not perhaps as close a network, so I think it's great that right here it's sort of this outset you've included us and there was this opportunity to continue to build these bridges. So I guess that's sort of one thought.

And I guess the other sort of sets of thoughts that I wanted to bring forward in terms of what have we learned or what have we done that we can inform what you're doing. So I think we're very sensitive to the idea that capturing exposures with devices right now is something that's very difficult and that's why it's very reasonable that you guys have developed this idea of your approach through registries initially, and then perhaps later, when UDI becomes available, to build on electronic health records.

Areas where there is perhaps more opportunity right now probably have to do with measuring outcomes, and that's something that we're already working with CDRH to try to build that into Mini-Sentinel, so Mary Beth Ritchey from your group has been invaluable in helping us with that, as well as others.

And I guess the other thing that I would point out are the governance issues. I think there are already some opportunities for us to be continuing to work together in those areas. We've talked about how we want this to be a national resource, and so I think we have to figure out what the governance for that will be if this platform is going to be used to be doing comparative effectiveness research. That's something that we really have to think about, how do we want to make this available to groups outside of FDA since that's really not the main purview of the FDA, to be doing that type of work.

So I think those are things that we can probably be collaborating on right now, and we've already tried to make some inroads in building that. So those are the main thoughts that I had to start off.

DR. GROSS: Okay, thank you.

I wanted to give a little bit of context and learn from the lessons that the Sentinel Initiative has brought forward. And let me take a step back and ask the panelists what constitutes active postmarket risk identification? And the key word there, I think, is active.

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So if you wouldn't mind taking a stab at that, maybe starting with Eric.

DR. PETERSON: Sure. So in my mind, the active surveillance is more moving to the concept that rather than always looking for signals out there in the world and waiting for major problems to develop and put their head out there, that this is a system that actively searches out and tries to uncover problems that may not be readily apparent under existing mechanisms of detection, i.e., only when a problem happens.

So the degree to which we constantly monitor, in this case, devices -- we'll take that as an example -- once marketed and as they get adopted into routine clinical practice to determine whether or not those devices have unforeseen problems that would be only evident once out in the real market in larger populations and in more generalized use, as Sharon had pointed out earlier. That transitional state, and doing that as a sort of routine part of clinical practice over the lifecycle of a device is, I think, an aspirational goal that we need to get to. So that would be a start.

DR. RUMSFELD: Sure. Maybe I'll quickly share what we're doing that I would categorize as active device surveillance in the VA with two programs. And I think this might be a tale of both hope and one of caution.

The VA has a single national electronic health record; we've had it since 1999. We have an integrated healthcare system, so we also should be able to follow the patients. Now, I'd point out, before everybody

says well, wait, how is that going to help us, I would point out that with the advent of EHRs, the growing proportion of EHR penetrance in the U.S. and the promise of health information exchange, that we're closely coming together actually with the kind of system the VA has had.

So here's the hope. The hope is, is that we can do active surveillance. We do it in a couple ways. One is with pacemakers and ICDs. All veterans with pacemakers and ICDs are registered through a web application that sits next to the EHR and it is synergistic with the EHR. And we follow, can follow those patients with the promise of also having the EHR data and the longitudinal outcome data.

The second one is in our cath labs. We've taken it a step further. The downside to the web-based registration is that it's both manual data and true to say the patient has ICD and what kind. And it also is a little separate from routine clinical workflow. So we've also had to go, despite having an EHR for so long, we've more recently needed to build clinical applications in the EHR that help with structured data capture at the point of care, structured data capture at the point of care both for key clinical information but also device problems or device information and asking the clinicians have you had any problems with the devices at the time you're using them, as part of routine clinical care documentation.

The promise of this is great because you're getting it, electronic health record, at the point of care. The challenges are the following: What



are the incentives to the clinicians to either register the device, put in this extra thing, or document the problem with the device. We have had some success in the remote monitoring of ICDs and pacemakers, that is all patients are registered, get their remote monitoring, clinically. And in the cath lab, we've had success because it creates the note in the EHR for you and allows participation in the American College of Cardiology's National Cardiovascular Data Registry. So because it gets you in the registry and it gets your note done, that's good.

All good except for one problem, and then I'll hand off, which is we still lack enough device-specific data. We know who has an ICD, we know who has a pacemaker, we know who got drug-eluting stents, and yes, we have their clinical data and their longitudinal outcomes, but we often lack the specificity down to serial number, lot size, and the things that we would really need to do active surveillance, and that's where we need to go next.

DR. GROSS: Okay. So, Fred, from your perspective, what constitutes active surveillance?

DR. RESNIC: So I appreciate the opportunity to answer that question. You know, I think active surveillance, to me, is actually a spectrum. It's not really one thing. The aspirational goal that Eric mentioned and then the implementation in one of the most advanced integrated systems that we have, which is what John mentioned, sort of give you a target of where we could shoot, still with the challenges even in a system with an integrated

electronic health record system and a longitudinal care model.

I think that for active surveillance, it's really very multi-faceted and changes over time, given where we are today and the next few years to, let's say, a more ideal situation, which we hope for when EHR systems are really interoperable with the widespread adoption of health information exchanges and standards.

So right now, I think, what is active surveillance? I think it's a combination in my mind, for medical devices in particular, of using detailed, granular registries that have device-specific information and a whole lot of information about the implant, about the physicians' experience with that particular device, that over time -- initially, that that's really the only data sources that I think contain a level of granularity that allow one to ask the questions in an active way really are the detailed, large-scale registries that have really been pioneered by a couple of the medical professional societies.

Ultimately, that transitions to a notion where the registries are populated or supplemented or become concentrated so that there's a greater dependency on the interoperability with longitudinal electronic health records.

But I think there are other components of active surveillance than just obviously these data sources. I think there is a mindset shift that must occur from -- and this is just building upon what Eric had mentioned, from sort of a reactive model for how to consider safety questions which are

now arising from what is admittedly an incomplete passive event reporting system or sometimes amongst the most interesting trends are really identified by physicians who, in their own practice, have had an experience with certain devices that have come back to them. And that seems like a pretty -- it's a noble and nice thing that clinicians are paying such attention, but, of course, you're really dependent on this sort of almost anecdotal tracking.

On the other hand, there's an opportunity with active surveillance to change the model where every device of concern that is prioritized, that for which we can get the granular data or we can encourage the development of a registry to do so could be followed for meaningful, appropriate outcomes of both device performance and patient outcomes, and that that should be part of our expectation, that we would follow the device performance over time.

Again, I think, as I mentioned this earlier, we're all going to be patients, all our family members are going to be patients. I would want to know that there's a trend for a particular device, especially when there are alternative therapies available, on how well it performs. And I think it ought to be incumbent upon the public health system in this effort for us to change our model to, as a device -- and part of the total product life cycle, to inform the industry experts who could use that information to improve the device, to make sure the perfect populations are receiving the device that we, by

routine, follow the performance of devices.

And I think we also need, as part of active surveillance, to think about how one would interpret the signals, though that was apparently a controversial comment earlier today. Obviously, one of the big questions for us is how do we do up the framework so that the signals that might be developed from an active surveillance model, we can interpret appropriately. We have transparency, participation by all stakeholders, because it's all, as Dr. Krucoff mentioned, about the public health, and to the extent that it helps the device manufacturers improve their devices, it helps the doctors improve their selection of devices.

I think the last thing is that I think the tools exist today, already, and many registries exist today or could be fostered and nurtured so that a lot of this is quite obtainable and automated surveillance, that is, the routine use of statistical methods to do so are within our grasp and we shouldn't delay.

DR. GROSS: Rick, do you want to take a stab at it?

DR. KUNTZ: Sure. I'll be brief. These are all good comments.

I think that what you're going to see as active surveillance is a set of factors that are generally and prospective studies that are not in the passive, the clinical practice of data extraction. And chief among them, to me, is the ability to obtain a rate and to make inference on a referenced population.

To obtain a rate, we need good follow-up with high ascertainment to minimize, ascertain a bias. It's critical. It's probably something that's missing in most databases. You can't achieve a rate unless you know the denominator. And you have to be able to understand the referenced population.

If you do surveillance on patients in a clinical setting and require consent, then you're already restricted to the referenced populations you have. But whatever level you start the surveillance in, that has to be highly ascertained at a rate of over 95%.

DR. GROSS: And Mike.

DR. STEINBUCH: Thank you.

I think of active surveillance really as sort of three prongs, if you will. The first, making sure that you have the opportunity to fully leverage the data sources that you have access to and some of which may be disparate. And those would be like, for industry, a complaint intake system would be one. Of course, a comprehensive literature searching, medical claims that are available, electronic health record information, any existing or if not existing, new registry data that may inform and all of these together, I think, could be very useful as sort of that first prong to make sure you have those sources.

Then when you have those sources, the next part, of course, is evaluation. So for tracking and trending, there's a basic tracking and

trending, and then there's an opportunity to go beyond in proactive surveillance, which is really employing a variety of statistical methods to evaluate changes in the rates, Rick said. Got to make sure we have appropriate rates that are valid. Disproportionate analysis is just one of several.

And then the third is really to make sure that you have timely, sort of, escalation of a particular safety issue and make sure as well that there is the ability and that you're well poised so that you can promptly act and manage any potential emerging safety issues that arise.

DR. GROSS: So let me ask you a general question, given sort of the background statements.

What are the attributes of an effective active surveillance system? You've all touched on pieces of that, so if you were to develop a high-quality active surveillance system, what would be its attributes?

I'm sorry. I should pay attention.

DR. RESNIC: Taking a lot of notes, Tom.

So a lot of the attributes were actually described well by John about where we need to head, but we can think of the attributes using the three-pronged approach. So there's the data source, there's the evaluation methods, and again, there's the sort of framework for interpretation, communication, and action.

And in terms of the data sources, I really, truly believe that we

need very detailed datasets that allow for appropriate adjustment for the complexity of why a certain patient would get a certain device and predict it to have a different outcome or may have a specific outcome, and so you really need tremendous detailed information about the patient and their condition that is not really contained currently in claims data.

We need very detailed information about the operator and the procedure for an implanted device to appropriately adjust for those factors that are related to the operator, the procedure, including the experience. And I think the notion of the learning curve is really a ubiquitous challenge for understanding the performance, especially the early performance, of medical devices. And you need details about the operator and the institution, if done in an institutional setting.

And, of course, we need to really understand the device beyond what -- the UDI allows us to identify the device. We actually have to understand what the device is. There are a variety of devices that are designed to sort of achieve the same clinical outcome, but they may have various human factor differences that would influence how we might expect them to perform, and so all these factors, the clinical/patient factors, the operator specific factors, the institutional factors, the device factors all vary by the device type and really the data source.

The second component is this notion of what are the statistical tools, and I do think that there is a whole portfolio available and, in fact,

healthcare, as is often the case, is sort of the last one to the table on this one. You know, you only have to go to the manufacturing industry or other safety oriented industries like Nuclear Regulatory Commission to look at the incredible statistical tools that are available to monitor for low-frequency events and then to inform, in a real probabilistic risk assessment point of view, whether a signal is worth evaluating.

I like the notion of prospective automated surveillance using either propensity matching or propensity survival analysis because it's easy to interpret, but I think there's just a huge variety of statistical tools, which is actually going to be a challenge because, I think, for communication purposes we can't invent a new method for every analysis we want to perform. There has to be some baseline analysis, and again, the framework has to be there as part of our active methods.

DR. RUMSFELD: So, Tom, a lot of this will resonate with what Fred Resnic just said, but I think that an active surveillance network or program at a mature level would have at least the following components: First, I cannot emphasize strongly enough my agreement that it has to be clinical data and granular clinical data. I don't believe that administrative or claims data can be effectively used because -- and it's not just about the characteristics of patients, indications for procedures, and past medical history, lab values and so forth. It's also the procedural details. To look for potential problems with devices or device performance without taking into



consideration what happened during the procedure, the results of that procedure, complications or difficulties using that device, or something that came up really muddies the water to understanding whether there was a true device issue.

The next linked thing is, I think, having more routine input from clinicians using the devices so it's not anecdotal, not just every so often we file this. Asking in a routine way, in care documentation and other things. This is a pretty straightforward one, which was did you encounter any unexpected problems with the device?

Longitudinal follow-up, I think, is -- we're talking about the ideal active system. I think being able to link this to meaningful patient outcomes, survival but also patient-reported outcomes, is ultimately critical because how else are you going to judge how important or severe or what was manifest from a potential device issue, those would be played out in whether or not it had an impact on patient outcomes.

The next thing would be unique device identifier. I think until such time as we have that specificity, that's going to go in the UDI, and as soon as it's ready, it will go into the VA data system so that we have that. We have trouble with specificity, again, about the devices.

And last but absolutely not least, Art mentioned twice is what needs to surround an active surveillance program. We could have all those things I just mentioned, and it may be useless if you don't have the right

governance or oversight of it. And I just would underscore what a big undertaking that is. It's been, just for the VA cath lab system, which is not entirely all the devices, obviously, medical devices in the VA. It takes having a dedicated program. It's both the analytic side of it, but it's also the patient care side of it.

What I mean by that is a lot of reports of device, potential device problems or potential device signals actually have a lot to do potentially with the people doing the procedure or risks of the patients brought to the table. You have to have the ability to know was there a bad outcome in this case; was it a clinical care delivery issue, or was it really a device issue? And to be able to evaluate that takes a real governance structure. And then you have to figure out how you're going to communicate those results both from a clinical perspective and to share with FDA, of course.

DR. PETERSON: So I'll emphasize a few things on the other end of it. We've spent a lot of time on it, and I would fully agree with the comments made about both the data needs, as well as the needs on analysis. But I'll spend a few minutes on the interpretation side.

You know, in science we're used to a few things. We want to get to the truth and the right answer. In this field, maybe that's the problem. And we want that truth to be whole today and whole three years from now or five years from now. Reality is, for this field, it doesn't quite fit perfect.

Partly, we wrestle with this idea of how much of this is the device and how much is the operator. Well, if you're taking a patient perspective, in a way, it kind of doesn't matter because something went bad and it involved the combination of those two didn't work out well for the patient.

But the reason why it is important to understand is partly this is risk mitigation; if operators aren't using it right or can be trained better to use them, that it isn't inherent and it could change over time. So there is the concept that, in fact, an answer today may not be the same answer it is tomorrow or years down the line. It could get better, it could get worse.

It could get better because providers become very passable with using this device and, in fact, you get down to some ultimately good result. It could get progressively worse if we now use it in different patient populations than we had in the past and the result in this new population isn't quite as safe as it was. So reality is it's not going to be the same answer today as it is years down the line.

The other thing is we want to get it certain that if it is a signal, it's a real signal. And there are lots of reasons why we do want that. Many people on this panel may have -- boy, they don't want a bad headline, nor do we want an idea of a bad signal being taking the device away from us. But that's only if it takes on the effect of once a signal comes out, it means this is a problem rather than, in the ideal -- in an ideal world, we want a direction.

It's the same as sort of in the current system, the inherent

suspicious of a physician. You see a couple cases, something is a problem, you raise it to the attention of somebody else, and eventually perhaps that signal is tested out and find out if your anecdotal experience actually pans out. This is more empiric, certainly, but it has some of the same characteristics. It's a signal. There needs to be further investigation.

Some of those signals will turn out to be correct, and we want a system ultimately -- we'd like a high percentage of those. But not all will, and that's okay. We should be accepting of a certain amount of that. We need to properly interpret when we have the early signals versus ones that we actually need to act on.

DR. KUNTZ: Yeah, I think these are great comments, so I want to repeat the ones that I think are really important for the elements. But I think I'll leverage off of what Eric said.

I think there are these situations where you want to get device performance isolated in addition to effectiveness, and they're both important. On the effectiveness side, the bell-shaped curve of different operators has to be taken into consideration, so if it can't be used by some people who are just too clumsy, well, then we have to look at those endpoints. But we also have to understand exactly how the device performs so we can actually make improvements in devices, per se, so one would be you have to be able to adjust for differences in either bad technique or operator issues.

And then there's the issue about comparative effectiveness. I mean, at the end of the day, we want to know whether or not we're making too much technology and is it better than something simpler. And I think that's probably within the environment or the universe of surveillance is that all those things are probably important.

But just a couple general comments about how one would go about looking at elements. I think what's critical is that all of the elements that we've talked about so far, whether it's, you know, the obtainment of a statistic, has to follow the highest level of methodology at every level, the ability to make inference, the ability to detect signals.

And one element I'm not going to mention is the electronic health record because it just seems everybody wants to get there. The electronic health record may be a dinosaur.

I don't know if you guys read Jacques Cohen's article in *The New England Journal of Medicine* a few months ago, but this is a pre-Internet vehicle, and we may be able to bypass EHRs specifically and utilize advance registry techniques, the Internet, patient networks and so on, and obtain a much more scalable system to get these goals than to have to force the square peg into a round hole in existing commercial electronic health record systems, which were developed maybe 30 years ago and still haven't advanced in their ability to obtain data.

DR. ARCHDEACON: So I think your question was what would an

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active surveillance system look like, and I guess the way it was sort of interpreted, I think, by a lot of people with what would a mature active surveillance system look like, and I think that's why I agree with what everyone is saying and why I agree with the concerns about use of claims data.

But I guess I just want to speak to, a little bit, as to why Mini-Sentinel right now has decided to sort of use claims data, and you guys will take or leave what you will from that. And I think one of the initial comments I made was this idea that the Sentinel system is sort of an aspirational thing, and do you ever arrive at this final system?

I think one of the lessons we learned is everybody wants this thing where you press the button and you get the answer, and we're probably never going to get there. One of these sort of overused cliché phrases that we've kind of developed is that we now talk about Sentinel as being one tool in the toolbox, you know, so that you have evidence before you go to the Sentinel system, and this advances you a little bit further towards the question.

And I guess I would really say I've come to think that there's probably going to be many tools in the toolbox that we'll call Sentinel. You probably would like to look at what question it is that you're asking and then decide which tool you want to pull out. And so there may be some times where we're not at a point where we have the ideal version, and so maybe it

is still worthwhile to try to develop some of these imperfect approaches.

You know, the Sentinel system 50 years from now might look something very different than what it looks like 10 years from now, but I wouldn't want to toss out the bathwater just yet and say that we need to wait for the perfect, perfect final system, and I do think it's going to be more of an iterative process.

DR. STEINBUCH: Just one last thing. I think the comments were really helpful.

And this may or may not be an actual attribute we touched on earlier with governance, but I do think that, from an industry perspective in particular, I think it's really vital that the collaboration, that there's a multifunctional collaboration between the quality organizations, medical, safety, engineering, risk management, regulatory and others that I apologize in advance for maybe missing, but the point, I think, as we well understand is that all of those functions really need to collaborate together to help focus on what is a true active surveillance system.

DR. GROSS: So, Patrick, I'm glad you commented upon claims data because I was going to ask you about different data sources. So am I to understand that claims data are sort of off the table? They're not to be considered as part of the active surveillance?

Sentinel is doing a lot of work in the claims data environment. They've validated claims algorithms. There are some hard endpoints that are

quite valid using claims data. So are we to, sort of, wash our hands of that, or what's your assessment of that?

DR. ARCHDEACON: I'd love to answer that. I think that this is potentially a philosophical view between drugs and devices. Since drugs have systematic effects, I think it's more likely to look at non-ambiguous endpoints that can be captured in claims-based data as a more relevant fit, such as stroke, heart attack, death, and others.

Devices are so specific locally, anatomically in effect and have complications and such with that, and they also have this other thing called the machine failure mode, which is something we want to understand even more so we can prevent clinical outcome before the machine fails, like increase impedance on a power lead before it fractures. These just simply are not captured in administrative accounting databases.

So it's not an issue of whether or not one can't use claims-based data. The current state doesn't map relevant endpoints to what, at least I'm interested in, in device failure, even from the patient perspective, compared to the more systematic and less adjudicated and ambiguous endpoints of the drugs that can't be captured by administrative databases.

DR. PETERSON: So I would say again it's not -- we're looking, again, to diametric choices here. It's not an either/or, claims or clinical. In an ideal world, I might argue, at least in the short run, that hybrids of those might be the superior model, and you'll be hearing over the next couple days



some nice talks that we'll sort of look at this concept of hybrid models where detailed clinical data are collected around a group of patients and their procedures and then potentially following those patients up, using the advantages of more ubiquitous claims and cheaper system.

But then, perhaps, as Rick has indicated, perhaps some degree of more due diligence once signals are detected, getting down to even CDC, of events that are potentially raised by these sites.

The other thing, too, is both are in evolution, right? The claims data itself are as ICB10 and other sorts, and now they're even generated off EHR systems, they're becoming better and perhaps more accurate in terms of both the detail as well as the accuracy of the information.

Our EHR system in Epic will generate our claims data. So it's probably one is a coded system of the other, it's not necessarily one is better or not than the other. It's improving while the degree of availability of clinical data are also expanding with EHRs.

DR. RUMSFELD: Yeah. Just also agree that that is not a matter of what's on or off the table. We should use everything in our arsenal. Patrick's points are well taken. I think where we have a hybrid approach is like the TVT Registry that Dr. Mack is leading and spoke about. We have detailed clinical data around the procedure, and there are claims or administrative data, and follow-up can be a very powerful model. Eric's points about the evolution of both claims data and clinical data are well

taken.

But being involved in an active device surveillance program across the VA with regard to the pacemakers and ICDs, as well as all the cath lab procedures, I will say that it has been having the clinical data has been the only reason that that's been a successful enterprise, getting down to understanding what actually happened with the devices, sort of, as Rick Kuntz pointed out. And I think we just should understand the importance of that. We're talking about specific device questions.

DR. STEINBUCH: I, too, think that the medical claims data can really provide lots of insights to supplement the clinical data, and I think that if one just understands what the limitations are and appreciates that, and has a really good understanding of the coding and the structure of the data that you're dealing with and be able to finesse some of the difficulties, I think that there's a lot that could be learned from it, and I think if we just throw it out, as somebody may have suggested, I would think that that would be a real loss.

DR. RESNIC: I don't think anyone said throw it out, but I do think that, as has been mentioned, having detailed granular data, clinical data, is fundamental to the analysis of the performance around these very complex procedures. If we think about the TVT Registry, it's 400 data elements. The PCI registry is 168, at my last count. That level of detail is, in fact, used for the adjustment, the appropriate adjustment of the differences

between patients.

I think the problem, if you don't use the clinical data as a fundamental building block, is that in the end you won't really understand what the results are saying because you'll be left with this huge question of confounding by selection, even just the obvious clinical differences between a patient who presents with a level of severity of a clinical illness that is not captured between coding differences, between unstable angina or non-ST elevation MI, but in the orthopedic space it's the same.

DR. ARCHDEACON: So I think, in the previous question, I think you did an excellent job of describing all the components of the system, and I guess one that just sort of occurs to me in addition to that right now is, we kind of realized that one final part of it is the people and training the people to use the tool appropriately. I think now we find ourselves in the position that we do have this hammer, and it's very tempting to go running around looking for nails. And probably -- I'm not in the device world, but I'm guessing probably most of your devices aren't really suited to be fixed with hammers. But maybe there are a very few.

So I guess the point I'm just trying to make is, I think, the same point that you were trying to make is you really have to understand what the limits of the tool are. And it may very well be, and I defer it to your all expertise, that the claims are going to have less value in the device arena that it will in others. I guess the key will be to make sure that we train both

people within the FDA and also the people outside the FDA that are looking at the FDA results as to what's appropriate and not appropriate when you frame the question.

DR. GROSS: Okay, let me take a different tack. We've all had experience with implantable devices, cardiovascular devices, sort of a narrow niche of the universe. So let's talk about active surveillance for ventilators or for infusion pumps. What does that look like?

DR. RESNIC: Well, what I think is interesting is that there is a lot to learn from "intelligent" devices and that, as Rick was pointing out earlier, you may, in fact, have a richer dataset that one can capture by getting the performance information off of these active devices, themselves, how frequently they may be alerting, alarming, or failing, even from the data that's tracked internally. Most of these modern devices are currently network capable, and I think there's a rich opportunity to think about non-implantable devices that are intelligent devices as being an enormously appropriate source of information for us to explore.

DR. PETERSON: So, Fred, let's push you a little bit on this, and maybe I'll have Rick next to you weigh in.

So now you're talking to Rick, and he has the ability to get remarkable degrees of data about his device and his device failure rate. Now, in theory, Rick can use that internally and you definitely would. But let's assume he starts to do a whole lot of analyses of these kinds of things.

What would be the potential goodness -- if you're Rick's lawyers, now, would you say that's a good thing to be doing all those -- you try to find where your device is failing potentially?

DR. RESNIC: I think Rick and his lawyers have an interest in understanding the performance of the devices. Rick, from a business perspective, wants to produce -- I don't think Medtronic produces ventilators, right? You don't make -- you do?

Okay, so let's just talk about the ventilator that Medtronic does not produce. I think it would be in Medtronic's interest to perfect the performance of that ventilator with as much information as one can gain over time. I do think, though, that there is an obvious challenge of this same information that can be used for the total product life cycle to improve the device could also be used as a hammer against the manufacturer for unexpected adverse outcomes.

Nonetheless, I think maybe Rick can speak to this, the late recognition of a real problem is a bigger problem; that is, that from a business perspective, not knowing about something until it hits the front page of *The New York Times* is, in and of itself, possibly a bigger problem not only for the patients who are affected by that device but all the patients who may not, in fact, have that device or the panic that ensues. So I think it is an improvement in public health and from a business perspective to know more about the performance of devices.

DR. KUNTZ: I think there are a couple questions here. One is are we interested in finding out if devices fail? Absolutely. I don't think any of my industry colleagues here wouldn't be interested in understanding whether they help or hurt patients, and if they hurt patients, they need to stop making products and selling them. I think everybody's committed to that aspect, very seriously committed to it.

So the idea of actually trying to survey is something I think we've missed, and I think it's something that all of us are intensely interested in doing because we need to understand what happens to our products in the market.

I think, Eric, you were referring to probably some issues of uncontrollable multiple comparisons and maybe some other issues that might lead to the chaos of trying to understand how to interpret data; the data may get out to the public who are going to have various levels of interest of interpreting potentially multiplicity analyses, and this is just the journey we all have to go through. We're trying to make a lot of efforts on the transparency side by making publicly available data. And it's like, you know, lighting a match in a cave. You don't know what's going to happen. If it's got a lot of methane, it's going to blow up, you know. And so we're pushing that to see what it's like to be more transparent and potentially deal with these issues of multiplicity.

But at the end of the day, we have to figure out what happens

to, I think, the original question. So we make an external diabetic pump, as was referred to earlier by one of the speakers, a continuous glucose monitor, and these things are highly complicated in understanding their performance. They have so much interaction with the patients. They get dropped into the bath, they get broken, and so trying to understand they actually work really requires a very sophisticated and also some data to understand how they can be improved, how we can relate what patients can expect when they get the devices so they can make an informed choice about whether or not they want to get the pump. We need to let them know that these are not easy to use and they're complicated. But that model on how to do surveillance, even on an insulin pump, is not established yet. It's very, very complicated to even work that out.

DR. RUMSFELD: Tom, just quickly. I would think inherent in your question is, is that when we have a procedure such as placement of an ICD, that may lend itself to -- and there will be a lot of talk about this in the next couple days -- having a clinical registry around that procedure. It seems unlikely we're going to have a clinical registry of IV pumps in the hospital. So what do we do about other equipment that doesn't lend itself to a separate registry? And I think that is a different model equally important for device surveillance, maybe even further away than where we are in these clinical registries.

What I would say is I think a couple of things may enable that

going forward, and they will have to be built in, but if we don't think of them ahead of time, it will never happen. One is that there is a real advent of, sort of, real time location systems, something we'll talk about again, I think, tomorrow, called RTLS. It can be barcoding or other things that identify where these things are. First of all, just knowing where they are in the hospital, where your IV pumps are or your ventilators. But then if you know where they are, it's at least possible to link that to "did we have any problem with them?"

This will take the cultural engagement of the clinicians, nurses working in the ICU and CCU to say did you, on your shift, have -- in addition to your other documentation, did you have a problem with any of the equipment, and then we'll have to integrate that, again, into the surveillance system. And for the patient use, devices increasingly used outside the hospital, a lot of care being hopefully away from -- outside the hospital, we need the same thing. We're going to need the systematic feedback from patients on what did and didn't work with the devices.

DR. GROSS: Okay. I am mindful of the time. I'm going to ask you one last question. This is easy.

During the course of the conversation, if you could refer to a framework for communication action. I think, Fred, you put your finger on it as well. So how do we govern this enterprise of active device surveillance? Do we all go off and use our own data sources and generate signals and



somehow deal with it, or is there an intelligent approach to the governance of this enterprise?

DR. KUNTZ: We're wrestling with that issue right now. Any device company who is actively engaged in trying to develop a surveillance program has to deal with exactly that. The optimum situation would be a partnership. I think that it's fair to say that there is not going to be any single way of doing surveillance. Nobody has the power or the money to do it all. And there's a strong responsibility of industry to do it because we actually make a profit on selling devices, so we have a certain amount of responsibility for paying for these therapies.

I think the model is going to be one of an ecosystem. Our version right now is that we would have the burden of data collection because we actually know a lot about the devices and what to ask for and how to collect them, and it's very important for us to feed that material back into the engineering design cycle.

On the other hand, decisions about which analytical tool to use, the interpretation of data is probably something that shouldn't be in the industry's domain. We'll certainly do it and try to act like good citizens, but there should be a totally independent viewpoint so that we can take our bias away.

Trying to understand how that works is very complicated, and it will take several years, and we're embarking on a variety of different models

to understand what it means to be responsible and work together, but it's got to be -- as Mitch, I think, said earlier -- it's got to be a system that works together in partnership, one with mutual trust. We've got to move away from this notion of having an academic agency kind of police, checklist, against the industry who always does bad things.

It's got to be something where we all engage in this together, we all understand what's at stake for us to win/lose. Winning, meaning that we're accurate in what we can say. And I think that trying to forge ahead of a variety of different governance models is going to be really critical. But as one member of industry, I feel strongly that there has to be an element of total independence on the interpretation of the data.

DR. RUMSFELD: I would only comment that we have tried, Tom Gross, with great credit to you, for just such a partnership of that between VA and FDA and then also bringing in the American College of Cardiology and CDR. We at least have those three together in partnership around the cardiovascular device surveillance.

And even that might sound very straightforward but, in fact, takes years to put in place the right sort of MOU, memo of understanding contracts, understanding the point that Rick just made about the data, who has the data, but I think the distributed model goes a long way towards that. It keeps things in the right place from a privacy and other standpoint. Then we can share results in partnership. And I think the only thing I would add to

that is probably heretofore in the VA experience, we haven't had the partnership with industry that we probably need, as well.

DR. STEINBUCH: The two T's that I think was touched on by Rick is that we've got to make sure that this partnership is really true trust and true transparency. And I think if we're lacking either or both of those, we won't succeed.

DR. ARCHDEACON: So I know there's been sort of one thought at FDA, at least amongst some people at FDA, that they thought of a metaphor; essentially, a national resources train, a railroad system, and there are multiple stations on the railroad and different people access it. So perhaps, you know, the FDA has one hub where it has access, but there should be other hubs, as well, where other groups have access.

And then I guess the thought that's occurred to us is perhaps what you really need is you need a third party to be running those hubs, so it's not that there's a hub for industry that necessarily industry controls, but there's some other third party, not FDA, not industry, and you sit there and you go, well, who could fill that role?

And I think we're still sort of searching for that, and that's the type of governance that we're trying to build, but I mean some players who come to mind would be PCORI, for instance, perhaps they could -- you know, they're sort of outside. They could perhaps play the role of a trusted third party. So I think those are some of the rudimentary ideas that we've been

playing around with. It's far from the finished product, obviously.

DR. PETERSON: I would just add a few minor comments.

Mike Mack gave a good example this morning of both the promise and the challenges that exist when he brought up the TAVI registry. I mean, it is a unique experiment right now, if we wanted to say that. You have all the right players, as we would at least think about being around the table.

You've got the major professional organizations, you have academics, you have the FDA, and you have industry, and you have CMS, the payer behind most of these devices, all around the table. I mean, it's a phenomenal experience.

On the other hand, the rules are not written of how we all engage in a way that's productive and successful. So watching this experiment, cultivating this experiment will be very important to try to get that down.

DR. GROSS: Okay. And on that note, I'm going to end the session. I thank the panelists very much. We could be here for another few hours. A lot of work to be done, but thank you very much. And I think we have a public session following, so thank you.

(Applause.)

DR. MARINAC-DABIC: As mentioned earlier this morning, we would like to give an extra opportunity to the audience to provide your comments on some of the questions that the panels had a chance to discuss

or on any other topic that you've heard during the day that you would like to provide comments.

So we now have one full hour to do that, and we're anxious to hear from those of you who didn't have a chance to discuss or participate in panel discussions throughout the day.

Much of the discussion centered around the governance of the system, of the organizational structure, of the roles and responsibilities of this national postmarket surveillance system. What we didn't touch upon is the accountability, the ownership of the system as we envision. So maybe if anyone would like to tackle that issue.

(Pause.)

DR. MARINAC-DABIC: Now, with Mitch on the phone and Sharon-Lise speaking to Rick. There are no usual suspects.

The important issue, I think it is that we have lots of lots of good minds in this room, and we discussed a number of very important issues. But I think it would be a really wise use of our time, during this last session, again, to hear from you to see if there are any other topics that we have not posed in our questions and perhaps to -- if there is none, then -- oh, there is one.

DR. NORMAND: End of the day, and I know Ted's going to follow and say whatever he's going to disagree with me, but nonetheless I'm going to say something maybe that might be politically incorrect, but I'm

going to raise the question.

And the question is as follows: Eric Peterson brought up the role of the professional societies, which I think is critical given that they certainly have the expertise and power and knowledge to develop the key elements to create these registries, and they certainly need to be front and center in them.

With that said, I'm going to say something that may be controversial, but one could also argue that there is some bias -- and we all have bias, I understand that and I hate that word, but in terms of perhaps analyzing or for certain aspects of this, one would worry -- I would personally want it disentangled from the professional organizations only to the extent that there may be issues with regard to certain devices, certain operators, things like that. So that's the one issue, one of the issues I'd like to raise.

And then the second issue would be -- and I know this might be minor, but I also wonder about costs of, let's say, the FDA asking professional societies to do analyses in terms of -- I think I've said this before. I don't think the FDA should have to pay for these things. I know it costs money because you're getting -- the professional societies have to have somebody run these things, but I worry about the costs in terms of who actually bears those costs if the FDA is asking for it, and second of all, the professional societies' investment into the process of looking at learning curves, et cetera.

So I'll just stop with that.

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DR. MARINAC-DABIC: All right, there we go. Professional societies.

DR. KRUCOFF: I'll protect her from disagreement, but I do think there's a really important point here. We made a little bit with regard to the question about what is it like to have FDA at the table and is it going to be the police or is it a scientific partner. I think we have to recognize that every stakeholder at the table has their presence and their evil twin sister.

So professional societies could be cumbersome, they could be biased, but that's not the face that we want to bring in. Professional societies have a unique operational capability and have the ability to orchestrate or convene educational dialogue so, you know, like building any team, in the industry, I think we can say the same thing. We can second-guess the industry's true motivations and blah, blah, blah, or we can recognize that the industry has all the genius that manufactures new devices and has the marketing capabilities that get them to the bedside.

So I think in convening a public-private partnership along the lines of this public health type of direction, we have to capture the strengths of every stakeholder, and we have to be very cautious about keeping their evil twin sisters out of the room. And I think that's manageable. I think we have to be aware of it. But I think everybody and every stakeholder has both of those possibilities. They could really screw this up, or they could invaluablely contribute to this, and I think the latter clearly is where the public

health interest belongs.

DR. MARINAC-DABIC: Thanks. Mike.

DR. MACK: Mike Mack.

So I would answer Sharon-Lise two ways. Now, one is absolutely the societies have a bias. Nobody is without bias. And the societies, as well as representing best interest of the patients, also represent their constituency, and that constituency has a certain bias to it. I think for that reason, in terms of putting this TVT Registry together, the analysis is not done by the societies; it's done by DCRI. So there is an independent, third party, respected organization that is doing the data analytics for it that is removing bias from it.

The second is I think that this is a multi-stakeholder, totally transparent engagement that keeps everybody honest and minimizes the bias with it. The analogy I think of is the heart team that we use for transcatheter valves, which a surgeon and a cardiologist go together to talk to a patient, and you each keep each other honest. As a matter of fact, you undersell what you're selling rather than oversell because you know the yang of your yin is there with you. So I think the same thing here.

You've got two professional societies that haven't always seen eye-to-eye over the years, and being in the same room and working together and now with all the other stakeholders from FDA, CMS, et cetera, I think it does serve to be a public-private partnership that everybody is honest



because -- and I should put industry in there, also, because they have been very engaged and very forthcoming and very open to this partnership.

So I think having everybody at the table and minimizing side conversations and having conversations with everybody present maximizes the chance of minimizing bias.

DR. MARINAC-DABIC: Thank you.

DR. BRINDIS: So Ralph Brindis.

And either I'm building or piling on. And I also want to acknowledge Sharon-Lise for bringing forward that point because I think, although you did it in a provocateur manner, it's a key point. In fact, you raised two key points that are worth commenting on.

I actually want to turn back to the FDA's point of view, as it came on. They said this is not "our." I mean, you emphasized that point a number of times. This is not "our" postmarket surveillance; this is "your" or "our" postmarket surveillance. And I think that shows, in depth, the inclusiveness that needs to be had for this to be successful.

Now, the NCDR registry, when it started, it initially was called the ACC NCDR. So in our wisdom, we think, we said this can't be about the ACC for us to represent the stakeholders, at least among clinicians in our early vision of what the NCDR was, which was looking at hospital quality and patient outcomes and clinical and physician performance. We needed to have a broad brush related to all the subspecialty societies and other

professional societies. That's a very early vision. The vision now is much different. And as Michael Mack so brilliantly stated, and with the partnership that we now have to have, it's not the professional society registry leading to what we need in postmarket surveillance. It has to be everyone.

And, again, I acknowledge what's occurring related to the TVT Registry, having many stakeholders at the table in government and in industry, and importantly, we're actually also having an advisory panel that includes patient groups and whatever. So we hope, as we learn together, stumbling along the pathway, that the vision that you have, that the biases that are inherent from any particular stakeholder running the show can be minimized by having these broad, collaborative approaches.

The next question, now that I'm up here, was the issue of the funding issue, and this is a huge challenge. I have to really acknowledge what the professional societies decided to do. They decided it was the right thing to put an investment to come forward and to develop these registries over time.

Well, we have different financial structures with which to keep them solvent. The mission related to postmarket surveillance involves a whole new business model that was talked about that we need to solve together. It can't obviously be on the backs on any single group. It's got to be a shared responsibility. Certainly, the professional societies cannot afford to do such.

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To be honest, we've been actually disappointed with private payers in our ability to get them to sit at the table. I don't know if there are any in the room; I'd love to listen to their comments because a lot of this information is of extreme value not only to CMS and then figuring out what to do related to patients and payments, but also to the private payer groups which have been reticent to be involved with us on these type of partnerships.

DR. MARINAC-DABIC: Thank you.

DR. LYSTIG: Ted Lystig from Medtronic, and I hate to disappoint Sharon-Lise, but I'm actually going to do a double negative and say that I don't disagree with her. I think the issue about -- in general, just in terms of where the bias is coming from.

And so, Sharon-Lise, you actually brought -- I think it was back in the March workshop, is that it's not simply the analysis of the data in which there was the comment about having DCRI involved in order to minimize the analysis biases that might occur, but it's also how the data is collected in the first place.

So if you have a group of persons who are performing procedures, and they're the ones who are assessing how well the procedures are being done, there's a potential there for there to be a bias in terms of how well it is being done. And we just need to be on our guard at all times in order to identify, minimize, and eliminate, where possible, subjective sources

of biases and try to find more objective measures so that we can make fair comparisons.

You know, industry, we ourselves are collecting data. It could be said that, well, you're collecting your own data so how are we able to trust that. And so part of what we do is we try to be very transparent about the methods we're using, and in some cases we might use external adjudication boards to say, "We've made this call, do others agree with us?" and try to create a scenario where it's not simply the analysis of the data, it's the collection of the data, it's the interpretation of the data, and give venues where you can make the best scientific conclusions from the data being collected.

And then I'll just bring up another point in that I talked earlier about the benefit/risk profile, and I would be interested in hearing if anyone would have something to share about means by which we can efficiently get at the benefit/risk profile across multiple therapy areas because I think there's great -- what we've seen for the obesity areas but I have a hard time seeing, so far, how that particular model could be expanded across the range of therapies that currently exist and will continue to come out. And so if persons are willing to give comments about how we can do that more efficiently, I think that would be a great topic for discussion.

DR. MARINAC-DABIC: Any other provocative comments?

(No response.)

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DR. MARINAC-DABIC: Are there any comments from the webcast audience? Ben Eloff, can you check? There are no? All right.

So can we maybe spend some time talking about some practical approaches to this? We started discussing the vision, we started -- everybody agreed with, almost everybody, with the efforts. We talked about inclusiveness, we talked about partnership or partnerships or consortium partnerships. We understand the need of working together.

Now, let's maybe spend some time to talk about what's practical and how this can be achieved. I think, from my perspective, we just need a couple or more champions, and we're going to make this happen, but those champions have to come from the key stakeholders such as industry; such as government, other government agencies; such as professional societies, academia, payers.

And I'd like to hear your thoughts on how you envision this evolving and what would be the reasonable short-term goals for this in terms of the timelines. We've talked about goals, long-term and short-term, but in terms of the timelines. So what's achievable given the fact that everybody is going to volunteer this; nobody's day job is going to be this, so we all have to work together in making this happen.

So from those of you who are involved in somewhat similar efforts in your areas of expertise, are there any experiences or best practices from getting this started? We've heard some thoughts from Mitch.

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Are there any other, maybe, representatives from other groups that would like to share some thoughts on how will this take off and what would be a reasonable timeline?

DR. KUNTZ: Well, I'll get the ball rolling.

So I work at Medtronic, and it's a large device company with a major interest in doing surveillance. So if we just use, as an example, about how we're going to try to enter into the arena and not try to wait until the perfect solution occurs, our effort is to the generalized use of registries.

So the goal is to expand the current surveillance we do to the more important and risky products to try to develop a scalable system for registries, which is not easy to do. It involves trying to contract with the single contract hospitals and networks, that the addition of new products would require just module additions. And we are also looking at experimentation with a variety of different electronic health record systems, most notably single payer systems like the U.K., in trying to understand how that system works. And we've got a couple of demonstration projects to understand whether or not surveillance can occur in that arena.

At this point, I'm not that excited about the potential for EHRs solving the device issues. I think that's been echoed by a lot of individuals here, and the notion that hybrid processes have to occur is likely going to be in the future. So it's complicated. If you try to do device surveillance, it's one of the most, in my experience, one of the most complicated research projects

you can do. And you can imagine the complexity.

So a company like ours has over 350 different product lines. We sell hundreds of thousands of products, if you look at the SKUs. We can't possibly do a registry on every one of those products, so we have to have a system that determines what's at risk and mainly to patients. So it's going to be based on the volume of sales and the kind of impact it can have on patients overall. To start there with a registry format in a more traditional sense is expensive, but we had to cut our teeth and try to understand how to get scalability and try to push the processes and understand these partnerships we're working through right now.

So if you're looking at whether or not it's receptive to industry to get the green light to push some surveillance, the answer is absolutely yes. Is there an existing plan, project outline to do this? No, there isn't. Can we turn a switch on digital medicine to get the answers? The answer is no. How are we going to get there in the future? The way to get there is to have a sense of urgency now to try to at least get some data, to try to put them in a format that people can understand, to try to incorporate as many stakeholders as possible for endpoints, such as PROs, and the experience will start to work. But, again, it's going to take a little bit of time.

We spent a lot of time talking about the TVT Registry and all of the effort of the stakeholders for one single product. Imagine trying to do this with hundreds of products. It's very, very complicated. So there has to

be a scalable system. Ultimately, I think we will have a digital solution going forward. I doubt that it's going to be the electronic health records that we have today. But that's going to be more of a Google solution with a variety of very advanced digital systems that we can extract, both inside and outside the clinical hospitals. And that's likely what I think will happen in the next 5 to 10 years. But in the interim, my bet is on more traditional methods for research that's scalable.

DR. MARINAC-DABIC: Thank you.

DR. SEDRAKYAN: Danica, I argue that you already started and make really strong steps towards this vision. A critical entity such as MDEpiNet and work with registries, facilitation of the Internet and TVT registries.

So I think the next step would be, I mean, this demonstration project style and in thinking about national priorities. Remember when comparative effectiveness became really high on the policy agenda -- important exercise of putting priorities out there. They're not really implemented widely.

But I think it's an exercise that is really good and important because we cannot build registries around every product and around every device and implantable/non-implantable. There will be confusion as to how big this effort should be. So targeted, I think, some priorities and some targeted structured thinking can definitely be a next good step.



DR. MARINAC-DABIC: Thank you, Art.

DR. LYSTIG: So I'll throw something out here for Art since we talked before about the registries, and that I think it's important to distinguish between a registry that is a census and a registry that gets information on some persons with a device. And I think that that tends to be confused somewhat.

I think that, in general, that we don't need to capture detailed clinical information with 480 fields on every single person that gets a device. I think that is nice when we could have it; it's extremely inefficient. We shouldn't need to do a full-on census.

However, maybe we can get around that by saying let's identify, in some cases, smaller subsets of patients for whom we can get full 95% ascertainment, we know exactly what did and did not happen with these patients, but at the same time if we're going to do that, we need to develop a system where there are other metrics, perhaps not the whole 483 but maybe 50 things that are measured regularly so that there exists a potential to go back into medical records captured on a patient for whom you can get the additional information.

So while registries will be useful, and while they'll be helpful, it's not something that for every single patient is scalable by any means but not even simply by in terms of across all products, but we should even consider should we be doing some sort of sampling of persons with the

device as opposed to every one for a certain class of devices. I know Art maybe wants to disagree in terms of numbers we need for adverse events that are rare.

DR. MARINAC-DABIC: Thank you, Ted.

Any other thoughts?

DR. KRUCOFF: Just maybe, again, a perspective that if we start by thinking about creating registries for device surveillance, then I think scalability and some of the other topics that come up are going to be required logistically to get anything going. If we start by thinking about capturing clinical practice, which is actually where many of our already operational registries are, then actually what we need in addition to that for device surveillance, it may actually be a much smaller piece.

So to what degree we're, again, in a public health focus, kind of say if we're capturing patient index hospitalizations and some procedural details because there's been at least a professional consensus that these are the things that, at a minimum, we'd like to know about the patient or about the procedure or about what devices were used during the procedure and about post-procedural events in the hospital.

And if we have other longer-term ways of capturing what happened to the patient, whether it's through clinic visits that are part of a different registry or claims data if the patient is 65 years or older or whatever, where we have really, for clinical purposes already, information,

then what would it take to understand by a little more specific device-oriented approach what device was used or how it's behaving. It may be that we can scale this a little differently if we start with what largely, at least, in some theaters, cardiology, orthopedics, I think are two, the clinically driven data capture registries that are already running.

DR. MARINAC-DABIC: Mitch, can I ask you one question? How soon do you estimate this postmarket system can be in place and to be called "our" and to be useful for all stakeholders with a module that will be specifically addressing the needs for a particular stakeholder community?

DR. KRUCOFF: Well, like everything we've been talking about, I think it really -- the answer to that question depends on which of the many questions you just asked in that one question you want answered.

To some degree, we have things that are already operational, and whether we could leverage them to a larger public focus, you know, to convene that conversation, my biggest tremulation there would be how do you deal with the lawyers, just to agree to do that. That's formidable. In other cases, if we really were going to build something from scratch in an area that we need it, that's new and different, that would take longer.

I think one way or another -- and I think Art said this before, I'm a great believer in proof of concept driven processes rather than trying to perfect all the processes and then put the devices in. So I think one of the things that early in this would help things move forward would be to actually

look around and again see who are the volunteers; where in industry are there devices; where in medical practice are there devices; where do we have new breakthrough technologies coming through, you know, in our universe, renal denervation, for instance, for people with hypertension; where do we have a breakthrough that's already occurred and now will start to be followed up, like transaortic valvular interventions; where do we have very mature areas but that continue to affect millions of human beings like drug-eluting stents; and look in each of those areas and say what would make this better, what data and whether we already have tools that are capturing data in these areas and what are the useful parts of what's being captured.

Is the quality what we need? Are the data fields what we need? And where there are deficiencies, what would it take to correct them and who would be interested? Is there industry interest, are there patient advocacy groups that are interested for diabetic devices, et cetera, et cetera?

So I think, if we look around us, we'll find that there are a lot of things already in motion, and depending on how we want to create deliverables, I think proof of concept driven deliverables will help us put novel processes, novel collaborations into place that then can affect other areas of electrophysiology or outside of cardiology, orthopedics; or if orthopedics has things going, that could affect or help us figure out what to do in cardiology.

So I'm a great believer in proof of concept helping us

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understand what we're actually improving in processes rather than to try and envision the processes, because I happen to also agree with Rick that by the time electronic health records are even as uniform as the VA electronic record is today, they'll already be outdated, and we'll have better tools that will probably be in every patient's hand.

So I think it's good to have a vision and put together a vision, but to try and create all the details before you actually take a step, to me, is backward and much more likely to fail than to look around for where do we have areas that are actually going that we can help and use them as proof of concept of what these processes and collaborative forces can do.

DR. MARINAC-DABIC: Thank you.

Any other thoughts?

DR. KUNTZ: Everybody's looking like when are we going to leave here to have our beer, but I just want to make one comment. This is just a comment. I don't know how everybody's going to react to this, but if we're going to advance the idea of surveillance, we have to address the issue of transparency, and it's a very complicated subject.

It's clear that, I think, from a business perspective, most providers in the device industry would rather put all their efforts in trying to define technologies and make improvements for patient care. Not worried about shepherding our data so that we keep away from the rest of the public, which is currently the state.

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If you move to a transparent state, we have to have a reform across many stakeholders, including journal editors, including the way we look at plaintiff attorneys, and looking at a system of transparency and methodology. A very simple reason why not to be transparent is that you're fearful of the method someone else will use and it will be disseminated without a clearer review of those methodologies. And it's a valid system. However, the transparency train has left the station. We have to become more transparent going forward.

So I think this is in lockstep with surveillances that, as we move forward and be a responsible group and start to make sure that patients, providers, caregivers are informed about their products, we don't have good transparency policies yet. And even in academia, there is a transparency cliff, right? If you spend all your time trying to develop and draw data, collect the data, create a network, process the data, you may not want to make it transparent immediately so that someone on the side can just get your data and start to publish on it.

So a lot of these thorny issues need to be worked out in order for us to get moving, but I think that it's an equally important area that has to be addressed as we move forward with the other aspects of surveillance.

DR. MARINAC-DABIC: Well, that's a really excellent point. As you know, we've invited the editors from *The New England Journal of Medicine* and *The British Medical Journal* and *The Lancet*, and I think

Bill Summerskill has arrived. I've seen him today.

So through all the next three days, I think there is going to be great opportunity, both in the MDEpiNet space and the registries environment, to talk about this very, very important issue with their input, as well.

All right. So if we do not have any other comments, I'd like to conclude today's meeting, again, with thanking you and inviting you to come tomorrow, eight o'clock, we're going to start our discussion on MDEpiNet with some interesting updates and exciting vision for the development of the MDEpiNet program.

And then the following two days are going to be devoted to the registries.

Thank you all very much. Thank you.

(Applause.)

(Whereupon, at 3:42 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

STRENGTHENING THE NATIONAL MEDICAL DEVICE POSTMARKET

SURVEILLANCE SYSTEM

September 10, 2012

Greenbelt, Maryland

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