THE BROOKINGS INSTITUTION

THIRD ANNUAL SENTINEL INITIATIVE PUBLIC WORKSHOP

Wednesday, January 12, 2011

PARTICIPANTS:

Welcome:

MARK McCLELLAN
Director, Engelberg Center for Health Care Reform
The Brookings Institution

Keynote Address:

MARK McCLELLAN
Director, Engelberg Center for Health Care Reform
The Brookings Institution

Sentinel Today: FDA Perspective:

RACHEL BEHRMAN
Director, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

JUDY RACOOSIN
Sentinel Initiative Scientific Lead, Office of
Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Session I: Mini-Sentinel Accomplishments and Plans for Year Two:

MARK McCLELLAN, Moderator
Director, Engelberg Center for Health Care Reform
The Brookings Institution

RICHARD PLATT
Professor and Chair, Department of Population Medicine
Harvard Medical School and Harvard Pilgrim
Health Care Institute

LESLEY H. CURTIS
Associate Professor
Duke University School of Medicine

KRISTEN ROSATI
Partner
Coppersmith Schermer & Brockelman, PLC

BRUCE FIREMAN
Biostatistician and Research Scientist
Kaiser Permanente, Northern California

* * * * *

P R O C E E D I N G S

DR. McCLELLAN: Good morning, everyone. We're going to get started in just a minute. I'd like to ask you to take your seats. We'll get started right now.

I'm Mark McClellan and I'm the director of the Engelberg Center for Health Care Reform at the Brookings Institution. I am very pleased to be welcoming you in out of the snow to today's Third Annual Sentinel Initiative Public Meeting. It is really good to see so many not only familiar faces, but faces who are leaders in many different aspects of issues related to drug safety, on getting better evidence on medical products, and it's nice to see this program which is now in its third establish something like an annual tradition with so many new things to talk about every year.

This is an extremely important topic and an extremely one, improving our ability to conduct effective and efficient surveillance of medical products, and products that people are actually using is a very important aspect of improving public health, improving decision making, improving the quality of health care and even avoiding unnecessary health care costs. I hope you will agree that after the discussion today thanks to the collaborative spirit, the collaborative public and private spirit around this set of initiatives we're seeing a lot of progress. It's a big and challenging topic but it's one that thanks to all of your efforts we're really taking on together.

As in years past, we're going to try and take stock and look forward at this meeting today. The purpose is to conduct an interactive dialogue between the FDA; the many collaborators with the FDA in implementing this new post-market active surveillance system and of course all of the stakeholder communities who care so deeply about these efforts. The specific objectives that we have today include discussing the

status now and the future plans for the Sentinel Initiative and engaging in a thoughtful and constructive discussion with all of you about that progress to date and about how to set and achieve some meaningful expectations for moving forward. This is a pretty large conference. Even despite the weather we filled up this room and we have an overflow room next door to welcome you and we'll be transmitting everything from in here to next door, it may be a little bit quieter, and we're going to I think need that space. But even in a conference this size, we're looking forward to the participation from everyone here. You all may have seen an earlier version of this agenda for our plan for today and there is one change here from that earlier version. That one featured a keynote presentation by then FDA Principal Deputy Commissioner Josh Sharfstein. As it works out, today is Josh's first day as the Secretary of Health and Mental Hygiene for the State of Maryland so that he cannot be with us this morning but certainly sends his regards.

After I'm done with these opening announcements and logistical issues, I'm going to make a few brief remarks that are going to fill in some of that slot by providing a little bit more substance framing the discussion that we're going to have during the course of the day and is also going to give us plenty of time for all of these very important topics.

After this initial opening, the FDA Sentinel Team is going to provide their perspectives on where we are now, where is the initiative today and where it's going next. That's the FDA's perspective on Sentinel today. Then we have a series of panel discussions with hopefully active participation from many of you. In Session 1, investigators from the FDA's Pilot Project, the Mini-Sentinel Project, will provide an update on their progress, including year-one achievements and the developments of the policies and tools and infrastructure that have taken place during the first year of Mini-

Sentinel, and then their plans for the year looking ahead. Again we're going to have plenty of time for questions and comments on these presentations.

Then we'll move on to Session 2 in which panelists from a number of stakeholder groups are going to share their perspectives and their thoughts on Sentinel's progress to date, future directions, key issues to watch for and suggestions for how to address coming challenges and, again, a lot of time for discussion of these perspectives with all of you who are here today.

Then in Session 3 we're going to hear from a panel of senior leaders at HHS and two large health plans about other federal initiatives that also utilize electronic health information for evidence development that are facing some of the same technical challenges and have some not unrelated goals in terms of helping to support better decision making by doctors and patients. This include initiatives for measuring quality of care, initiatives related to comparative effectiveness research, and because of the similar kinds of challenges they face both from an infrastructure standpoint and method standpoint and all the other policy issues involved, there may be some potential applicability of the lessons from Sentinel, the infrastructure from Sentinel, to support these kinds of purposes or reinforce all of these public health and quality improvement goals. That's the outline for the sessions for today. Again this is a large meeting but we're going to run this with a significant role for active participation from all of you and I'd like you to keep that in mind.

That brings me to a few housekeeping comments for today. One is that this is an open and public meeting as part of FDA's commitment to an extensive and transparent process for implementing the Sentinel Initiative. Press have been invited here today, the workshop is being recorded so that everything said here is going to be on

the record. The presentation materials from this meeting will be posted on the Brookings website and on the Sentinel Initiative website within the next few days and will be available to everyone, even those who couldn't make it.

For those of you who are panelists today, I'd like to make sure you know Michelle Wong. There's Michelle right there in the front row. She's very nice. But it's also her job to make sure that we have plenty of time for discussion during these sessions so that she will have a signal for you when you're approaching the end of your allotted time and we'd like to try to keep to that as best we can remembering that with all this time for discussion that will be a lot of time for more details to come out in the discussion part of these sessions. The opening comments that you're going to hear from all of our panelists are just meant to set the process going and get some key ideas on the table and we want to focus on that discussion and back and forth part of the meeting.

Panelists also be mindful of turning on your microphone before speaking. I think there are some switches on these and hopefully those will work smoothly during the day. Also throughout the day there are going to be many opportunities to ask questions as hopefully I've made clear from this overview. If you have a question or comment, please wait until we get to that part of each session and then we'd like to move through these as efficiently and constructively as we can. When you get the microphone, please identify who you are and please try to keep the question and comment as concise as you can. I know a lot of you have important, significant and meaningful views about how some of these Sentinel issues should be addressed and we certainly want to air those as well, but we are going to try to do this in a way that respects the limited amount of time and large number of people that we have here today and the large number of issues that we want to discuss as effectively as possible.

Also if you are in the overflow room and you want to participate in the Q&A part, there is a dedicated microphone or there will be in the back of this room for everyone to use so that just because you're in the other room doesn't mean you should not plan on participating if you have a comment or question to include.

So that's where we are in terms of the meeting for today. Let me pause there and make sure I didn't miss anything about logistics. Again thanks to everyone for coming. This is not ideal Washington weather and it's probably not ideal weather from where you were coming from as well and we have people who made it out of Atlanta which is very impressive to get to this meeting. We really appreciate all the participation. This has been a tough week in a lot of ways for many people in the country and this is the kind of public-private collaboration that I think gives me a strong sense that we can accomplish a lot together so that I appreciate everyone being here and contributing to try to move forward on these critical issues.

Now instead of a keynote address you're going to get a little bit of a brief overview from me of some of the topics that are going to come up during the course of the day, some of the progress that's been made and some of the issues that we're dealing with. With a group as diverse as this, with some people who have been devoting their lives to active post-market surveillance issues over the last few years, people who have lots of interest in health care policy but haven't been as focused or haven't had time to be as focused on Sentinel and this particular set of projects, I'm going to try and provide a bit of an overview and update that hopefully provides a little bit of something for everyone. I think my staff overstated this a little bit by calling it a keynote address, but it is going to provide some context for the course of the day and hopefully get us off on all of the key issues that we're going to try to address that, and that is toward this goal of

better post-market evidence for medical product safety and the key role of this set of initiatives in our nation's broader public health and health care improvement objectives.

This is a little bit of a complicated chart but I think it highlights just how much as been going on since the legislation creating FDA's new initiative related to Sentinel and FDA's new post-market activities which began as part of the 2007 Food and Drug Administration Amendments Act. That act mandated that FDA develop a system to enhance their ability to monitor the safety of medical products once they're on the market and it was envisioned to be something that would complement FDA's existing system, spontaneous adverse event reporting, Phase IV studies of the more traditional type, not to replace it but to provide a more comprehensive set of tools and hopefully work synergistically with some of these other resources that were available.

As you can see from the slide, there have been a series of steps to lay the groundwork for the Sentinel system over the three years since that law was passed and what you're going to hear about in more detail today is how these components of Sentinel implementation have moved forward, and I think very importantly how much they represent a real collaboration between the public and private sectors. In fact, one of the first things that was launched after the FDA Amendments Act was passed was a privately led effort, the Observational Medical Outcomes Partnership, which had participation by FDA and a range of independent experts and has focused on a number of the technical challenges, statistical challenges, data challenges, data aggregation challenges and the like, that underlie the implementation of a program like Sentinel.

This is not straightforward work. The data systems involved are diverse. While large numbers of patients and large numbers of users of medical products and large potential control populations can be included, they are typically in observational

settings and sometimes without consistent or as complete information on clinical details as one would like. They raise a number of technical issues from a data standpoint, the aggregation standpoint and the statistical methods standpoint and OMOP has taken a number of steps to identify and then take on those technical challenges to provide some technical insights about how these efforts can be most forward. Many of you here today may have participated in OMOP's annual meeting over the last couple of days where a lot of these issues were discussed and again a lot of progress has clearly had an impact on some of the other steps on this timeline that OMOP has continued its efforts throughout this three-year period.

Also in the course of implementing the Sentinel system, FDA contracted to develop Mini-Sentinel. That's a pilot program that will inform the development of the Sentinel system. That contract was developed over 2008-2009, there were some pilot contracts awarded as a prelude to that and then the Mini-Sentinel contract was awarded in 2009. It's a partnership between the FDA, Harvard Pilgrim Health Care and a range of other institutions, including HealthCorps, the Kaiser Foundation Research Institute, Humana, Rutgers, Vanderbilt, the University of Pennsylvania, the University of Iowa, Harvard Medical School and many others. I could go on. So it's a very broad-based effort to help with implementing some initial pilot versions of Sentinel activities. Along the way obviously there have been a lot of other activities and opportunities for input for trying to develop the key ideas underlying the Sentinel program.

These opportunities include some of the forums that we've been involved with and I'll say more about those in a minute, a series of other public workshops and FDA-led stakeholder meetings, a lot of efforts to try to bring forward ideas because again there is really no way to implement this program without public-private collaboration.

Those stakeholder meetings and these early workshops and these early pilot steps identified a whole host of issues and challenges that would need to be addressed to developing more effective and confident capacity for meaningful active post-market surveillance. As I said, they also highlighted the value of a transparent, collaborative process involving a broad range of stakeholders to help bring this effort together providing not only comments and ideas but for many of these stakeholders, active involvement in leadership. This isn't a project that is or can be conducted by the FDA. It's required real technical input, hands-on sweat equity from many of the stakeholders and many private-sector participants in this effort to solve the challenges.

We at the Engelberg Center are trying to help support this kind of participation and reinforce this process. As I showed you on a previous slide, we convened a number of meetings and workshops to discuss particular issues, to look for practical solutions and discuss and debate those kinds of solutions for developing better post-market evidence. I think these ongoing efforts, ours and those sponsored by others, are important mechanisms for developing the ideas on post-market surveillance and it's also included a lot of opportunities for experts from outside of Mini-Sentinel as well as patient and consumer advocates, representatives from industry, health care professionals and others to participate in this process.

Among these different activities have involved our roundtable webinars. These are still ongoing and I would encourage those of you who haven't participated that it's a good way to hear about some of the many activities taking place around the country again many of which are outside of Mini-Sentinel and outside of directly FDA-sponsored efforts but that are still relevant to this whole set of issues related to post-market safety and better evidence on medical products. These webinars are open to the public, we

have more coming up soon and we'd delighted to have additional participants.

In addition, there have been a number of expert workshops. These are typically very technical discussions of particular near-term challenges for active surveillance implementation. Some of these have included things like technical methods for implementing a network infrastructure. This workshop explored the feasibility and requirements for using a distributed data network for active surveillance and I'll talk about more about that in a minute, the tools that are required and the issues that may influence data and analytic partner participation.

Remember that this being a partnership, one with active work required by the participants, the data holders in the effort, need a process to make sure that works for everyone and is sustainable so that those network infrastructure issues are very important early on. There are legal issues and these are extremely important, issues like protecting patient privacy and confidentiality, issues like addressing potential liability issues that may arise in the course of evidence development which is at least in process and not always complete and not always definitive but can still raise liability issues so that those are very important to address. Clearly methods themselves for working out potential signals and identifying them and strengthening them for reaching more definitive conclusions, an area where OMOP has also been very active.

Finally, another critical topic is how, when and to whom to communicate findings from active surveillance again since the answer aren't always completely clean and arriving on one specific data with major insights that never were there before is much more of an ongoing and incremental process in many cases. So there are lots of activities related to expert workshops.

Implementation meetings. These involve convening groups of senior

leaders from both the public and private sectors to explore upcoming issues related to implementation looking a year or two ahead at what needs to be addressed and trying to discuss it, plan for it and make sure that all of the key implementation challenges and ways to address them get on the table. Some of the previous meetings here have included discussions of different organization models for the Sentinel systems as well as ways to ensure meaningful participation from data and analytic partners.

Then finally and very importantly for today, our annual public workshop. So that while there is a lot going on obviously with FDA, Mini-Sentinel, other Brookings activities, other organizations, there are a lot of websites that provide regular information about Sentinel's status, this annual meeting is intended to try to bring all of that together for people who may not have time to focus on this all the time or who are maybe focusing on specific issues but want to take a step back and think about the big picture of where things are and where they're headed. This annual meeting is intended to provide an opportunity not only to step back and think of where Sentinel is and where it's going overall, but to provide an opportunity for a broad base of direct feedback on Sentinel's direction to the FDA, to the Mini-Sentinel investigators, to everyone who is involved in this very important and very challenging effort. We have more information available on all of these issues on our website and again I would encourage those of you who want to do more or get involved more with Sentinel activities or at least be up to date on what's going on with them to think about ongoing participation in some of these other activities.

Thanks for the contribution of a lot of people in this room, as we'll hear about today there has been a good deal of progress toward achieving the goals of the Sentinel Initiative. In fact, in conjunction with this meeting this morning, and this kind of timing never works out, we've very pleased that the *New England Journal of Medicine*

has published a perspective from FDA, Brookings and the Mini-Sentinel team outlining the structure and function of Mini-Sentinel. It's been a good complement to the updates that you're going to be getting at this meeting today. The article is available on the *New England Journal* website starting this morning and we're going to try to make copies available to all of you who are interested in getting one before lunch. In this perspective we talk about the process that was used to create Mini-Sentinel's distributed system which is now operational and capable of querying potential safety signals on over 60 million patient lives. It describes Mini-Sentinel's ongoing and future priorities. It emphasizes the importance of stakeholder engagement as we've talked about already for providing not only the ideas and the pathway to effectiveness but the momentum for this kind of public-private initiative to continue and succeed. Then it also highlights Sentinel's potential as a key foundation in a much more effective learning health care system. It's a distributed system. There's not one database somewhere. But it's quite a remarkable resource for gathering evidence and for learning more from the practice of medicine and from the practice of health care in this country.

Mini-Sentinel is definitely a work in progress, but as the article highlights all the work that you have contributed over the last several years, it makes clear that there has been a lot of progress and some key features are now clear and that's what I want to talk about now and again we're going to discuss a lot of that in more detail during the course of the day. But in terms of some of these key features, first the framework for Sentinel is clearly a distributed database network. That means there is not some central warehouse or data repository somewhere where everyone's information, increasingly complex information, gets dumped and held. Instead, the underlying data used in the project stay with the data owners, the people who are actually using these data for the

delivery of health care, the payment of health care, for actual health care activities in some way.

The basic idea here is if there is an interest in a safety-related question and it's an oversimplified version, the basic idea is to try to find among all these data partners a common way of defining say a numerator and denominator, a denominator of all of the individuals who might have been exposed to the medical product and a numerator out of those who had some kind of significant adverse event. The basic idea of this network is if everybody does that the same on each of their own data, then the summary information coming out of that, the numerator and denominator, can be combined. It's more complicated than that in practice, but that's the idea, distributed data that stays out in the cloud or in its own homes wherever the data are and it's only brought together in a summary fashion to answer the relevant questions for safety and effectiveness.

Of course going along with that, to confirm the cases, to take further steps, there's going to be the capacity to trace back to the original data holders and the original data itself to confirm cases and things like that. So you can think about this as bringing the policy question or the safety question to each data source rather than taking each of the data sources and bringing it to the question.

There are some clear advantages of a distributed network and these are the reasons why things are evolving the way they are. Each of the partners in this analysis maintains control of their own data because they're close to it and they help make sure that their own data aren't being misinterpreted. This also helps with important privacy protection since the individual data are staying where it's being used for patient care already. This does create some challenges, too. There is real work needed by

analysts at each of these data sources, real involvement on an ongoing basis and that's why I've been emphasizing partnership and the need to create momentum and a sustainable infrastructure for all of these participants to continue to participate actively. It does require some real work on their part. And there needs to be a process to get agreement on consistent methods that can be applied across all these sites to get to meaningful results with this system and also the limitations of those methods needs to be commonly understood by the whole environment by the whole set of participants.

In this approach it is critical to collaborate effectively with a wide range of stakeholders, health plans, integrated data systems, health care providers with electronic records or supplemental information that's needed for investigating a safety question. They are all analytic partners. They're not just data providers into some warehouse. It's an analytic partnership, a distributed analytic partnership.

This has led to a number of issues and a number of challenges and real hard technical problems for implementation which are being addressed but which are certainly not fully resolved and are still part of the ongoing Sentinel implementation effort. Some of the issues that the FDA and its collaborators on active surveillance are still working on include developing a generalizable framework for refining safety signals. What does the science of active surveillance really look like? Developing established protocols for answering common safety questions. With this distributed network, the more there can be common, well understood, validated accepted procedures, the smoother this whole process will go in terms of addressing each application, each safety question, in an efficient and timely way.

Also important is having a mechanism for continuing to solicit input from experts in the public to continue to improve the rigor and the credibility of the methods

and results. OMOP has been doing a lot of work here in supporting the technical side of things as well as many of the investigators inside and outside of the Mini-Sentinel project, but without question there are many technical and statistical issues that still need further work and we'll talk about some of those today too.

Then very importantly, developing strategies to educate health care professionals on how to interpret and to apply the information from active surveillance along with all the other sources of evidence that they need to keep track of and keep up to date on so they can in turn help patients make informed decisions about their care, and similarly I should say education for patients and consumers about what all this evidence means for them and how they should interpret steps and reports that come out of the active surveillance system again are not always going to be completely definitive that all of a sudden we didn't know anything and now we know everything about a safety question and that's not the way this ongoing active surveillance system is likely to work. A lot of those issues are things that we're going to cover today because there are ongoing challenges and ongoing areas that active surveillance needs to address.

It's obvious in all of this that continued engagement with the wide range of stakeholders who care deeply about these efforts is going to be essential to the overall program's success. Stakeholders like the people who you're going to be hearing from today have an important role to play in providing guidance and insight and helping to help realistic expectations for patients, the public and for lawmakers about what Sentinel can and cannot do. There are also significant implications for medical product developers who have a major interest in better evidence related to the safety and effectiveness of their products. Health care professionals have a huge role in interpreting this evidence as I just described. And finally, patients and consumers need to be involved throughout

the process to help set priorities, to help ensure that health information is used effectively and appropriately and to ensure that the activities and the results of active surveillance are communicated effectively.

The Sentinel Initiative is developing at the same time as many other steps are taking place that are intended to provide better evidence for decision making. Recent legislation and many private-sector initiatives are exploring and expanding the development and use of electronic health information to answer a broader range of important health care questions to provide a stronger evidence base and strong decision-making support for doctors, patients, health professionals and others in our health care system. There are a number of issues that arise when health information is used for purposes like this, purposes other than direct patient care. These secondary uses of health information are potentially important but they raise a number of also important policy issues and those are still very much being explored and are going to be over the next couple of years. What gets all the press these days is the health care reform legislation in terms of expansions of coverage and new subsidies and so forth, but this is also a critical time for evidence as we're moving to a system that really has potentially much richer data but with data that presents a lot of questions about privacy, about appropriate use and appropriate methods for using it and about bringing that information to bear more effectively for better decision making. It's a critical period for evidence in our health care system as well, and the Sentinel system is really a unique part of that because it is so extensively developed already thanks to the efforts of here.

Again, there are 60 million participating in Mini-Sentinel, large efforts using public-sector data as well so that potentially an important foundation for how these kinds of policy issues can be resolved in other settings related to better evidence in our

health care setting as well. All the work on data infrastructure, privacy and security concerns, development of appropriate analytic methods, participation of data partners and analytic partners on a sustainable basis, all these issues that Sentinel is dealing with I think have important implications for these broader challenges facing our health care system. Of course, the big issues that still need to be solved go to those other areas as well for things like effectiveness research, quality measurement and reporting, creating a sustainable mechanism for participation by data and analytic partners, developing active public-private partnerships that are governed effectively, extending our capacity to appropriately link and analyze different data sources while protecting patient privacy, ensuring all stakeholders have meaningful roles in these activities, they're challenges for Sentinel and they're challenges for the rest of these other key activities in our health care systems.

So that's why today is so important, not that we're going to solve all these problems, but you have an opportunity here today to participate in right now what I think is one of the most important set of initiatives related to these core issues for the future and wellbeing of our health care system and for the future health of Americans. So today is a very important part of this process of moving toward better evidence, more personalized evidence on safety as part of moving toward a much more effective, efficient evidence-based health care system and I want to thank you all for joining us to participate in that effort.

That brings me to end of my opening and framing remarks. We're not going to have questions and discussions of this because what we really want to focus on is the panel presentations where all of these issues and I'm sure many more are going to be discussed I think much more extensively and eloquently than I've been able to do in

these short opening remarks. I'd like to move right on to that right now with our first set of remarks on Sentinel Today from the FDA perspective so that we're going to hear a few words from some of the leaders at FDA on this effort. That includes Rachel Behrman, director, Office of Medical Policy at the Center for Drug Evaluation and Research, and Judy Racoosin, the Sentinel Initiative scientific lead in the Office of Medical Policy, the Center for Drug Evaluation and Research.

Rachel and Judy, come on up and let's get started with your perspectives. Thank you.

DR. BEHRMAN: Good morning, welcome. Actually, Mark's covered pretty much everything, so I can just say ditto or choose to emphasize a few points. I will choose to emphasize a few points.

First of all, on behalf of the Agency I would like to add our welcoming thanks to everyone who has for the past three years been marching a long beside us, so, certainly, patients and consumers and their leadership representatives here today, and our data partners without whom there would be no initiative; our colleagues from OMOP; our colleagues from regulated industry; our colleagues from Boston, from Harvard.

And just as an aside, I'd like to say that when we think about causal relationships, ever since we started working on them there has been a substantial increase in the amount of snow in Washington. So is that right? Is that a signal we should pursue or not? And if so, how? What are the methods that would help us determine whether or not it's correct?

And, obviously, our colleagues from Brookings without whom we really would not be where we are today. I mean Mark put up that time, sort of a timeline, and what was not shown for the right before the official relationship with Brookings was the

invaluable assistance Mark and his colleagues provided to us right from the beginning. I guess it helps to be an ex-FDA commissioner as well as health broad perspective on health care.

So we stand here three years later at our annual meeting much farther along than I would have expected, and I'm delighted to say that. I think that thinking back in, at least in my years of federal service which at this point are amazingly 20, the only other time I saw this kind of really rapid progress which was accomplished only through collaboration was something Mark has emphasized repeatedly, and appropriately so, was the early, early days of HIV drug development.

Now, there, there was an obvious or what people perceived as an obvious tangible threat by a virus, a deadly virus, and everyone could coalesce or collaborate around that threat. Here the threat, and I think it's quite real and in a way much more impactful, is much harder to articulate it. It's the I don't want to say crumbling of -- or would it be fair to say crumbling of our health care infrastructure and our ability to deliver care, our ability to afford to deliver care in the way we as a country want to and should? That's a real threat, but it's much less dramatic than a virus, and yet, from the beginning we have had aptly the Agency, the Food and Drug Administration have had absolutely no trouble engaging the communities that need to be engaged and want to be engaged in helping us move this forward.

And, Mark, there are two points with which I want to quibble. One was you said no way to implement without a public-private partnership, but three years ago that was absolutely on the table as a question with a big question mark, and I think we have proven -- so the first thing and harkening back to Mark's comments about it's been a tough week, and when we see forward progress like this, it makes us very hopeful -- we

can't fix the entire world, we can fix a piece of it. I think we have proven in this, in this collaboration -- I'll talk a little bit about the specifics -- we've shown that the federal government has a better way to function; that had we gone it alone and done it in silo which -- and there were advocates for that -- we would not be where we are today. And instead, we are far ahead of where we could have imagined being and have a much richer, more productive and more effective program through collaboration.

So, Mark, I think the answer is, yes, we now know there's no way to implement it without public-private partnership. I think that was in question three years ago, and we've answered that question, and that, we hope -- we'll talk today -- can dramatically influence the way other parts of the government -- the Agency, but other parts of the government -- think about moving forward on related efforts.

The other piece I wanted to quibble about was the distributed model. That again is a serious question three years ago. Absolutely on the table, now it seems, as my children would say, like a no-brainer. So things that seemed insurmountable, problems that seemed insurmountable three years ago -- and I'm looking at Kristen and I'm looking about some of the privacy issues where we just were all holding our heads in our hands -- we've gotten way past the discussion about oh, my goodness, the data can never, ever, ever move, to how do we protect it? How do we protect the patient and the consumer, but how do we maximally protect them by making sure their information is being used optimally? And thinking creatively about what is involved in that.

So our discussion has become far more sophisticated and far more productive. So that talks about the partnership that we have, one thing we have accomplished, because this is, I think, the first meeting where we're actually talking about tangible deliverable accomplishments. The first meeting was if you will meet and greet.

The second meeting was a little bit more priority setting. I see (inaudible) nodding her head yes. This meeting is the first time we're actually presenting results. Now, that doesn't mean I'm going to tell you Drug A causes B, although I do think working with Rich does cause snow in Washington, but that's my opinion. And, therefore, I think the Harvard crew should come and shovel my driveway when we really get dumped on.

But so we -- I think we've answered the partnership collaboration question how to fully operationalize that is not -- is a work in progress, as was proven last night, as we -- past -- personally past my personal bedtime -- but we were still struggling with some slides because one thing we learned was that we're very used to working in a regulated industry, and we have a language and systems in place. Now we've gone to a different community, the academic community, in a different way.

In other words, we're not reviewing your INDs and your NDAs as we usually do. We're very, very different. We've learned how to learn to develop a language and methods and so forth. And what is obviously sensitive to us is not obviously sensitive to a different community and vice versa. And we're having to learn to be very sensitive to those issues because those become stumbling blocks and ultimately could become deal breakers if we don't fully understand the priorities of each sector and make sure that they're articulated and addressed. Not everyone gets everything they want.

We all have to lose some of our, if you will, autonomy, but at least we have to think it through, make conscious decision, make sure it's on the table, and then move forward. Otherwise, if we don't understand what brings people to the table and what drives them away, we no longer have a collaboration. And in that sense, Mini-Sentinel and Sentinel in general is a very good work example of the kinds of things that

we need to work through as we move forward.

And I'll talk in a minute about where we're headed, but I do want to spend a couple of minutes on communications. Mark touched on communications in one way, which is -- and we follow and talked a lot about this: How do we get this kind of data out there in such a way that makes sense, that's not misleading, and it's constructive? In other words, again saying that because we're working with Harvard we're getting snow, if it were on the more serious subject that could be very destructive. We'd say, okay, fine, we won't work with Harvard anymore and we'll solve the snow problem. But when you talk about a drug and misinformation or partial information or confusing information kind of filtering out, that's a serious problem for us.

Now, we -- FDA -- have maintained and are convinced we -- not that we're such experts at communication, but this is not a different problem for us than we have every single day, but working in this environment is very different. And that point was driven home by the press reports this week about the saxagliptin study. And you'll hear a lot more about that as a methodology in a little while, and I'm not talking -- I'm not going to be talking about methodology other than to emphasize that the methodology is in its infancy.

We really don't know how to do this, so we have to learn as we go. But we chose this Saxi study very, very carefully. Judy Racoosin, who's our scientific lead in collaboration with the Center, put together with the candidates, we went through them; but one crucial point that was missed is, what was absolutely critical is that -- as Judy likes to say -- what's the plan? Well, the plan was that there's an ongoing randomized control trial. So we have a plan. We have a safety net. If we don't understand the information we get, we will have other information such as if we wanted to go back to my

snow example, we look at the *Farmer's Almanac*, we could really figure out if indeed there is to be more snow.

So the press reports that, I don't know, just said we chose Saxi because it was diabetes, chose Saxi because MIs, chose Saxi because we thought it would make Congress happy, chose Saxi because we wanted to pick on those particular companies, whatever. They weren't quite right, and we have to figure out how to operate in this collaborative environment. Our thinking will not always be that clear, but at the end of the day, because Mini-Sentinel is a contract from the federal government and from the Food and Drug Administration, we will make certain decisions, and we will make those decisions as transparent as we possibly can. But there will be times when we won't be able to be completely transparent, and that is the truth.

The next point I want to make is similar, similar to that one. It talks about managing expectations, and Mark touched on this as well. Sentinel, it's not in its infancy anymore, I think we're all the way to toddlerhood, but we are learning how to do it. And we have to somehow make sure we always communicate that, that as we now do talk about results, and as we do talk about developing methodologies, we're very clear about what the limitations are, what we can and can't do, keeping our eye on the future, not only building toward the future, building towards this national resource, but we're going to have concrete deliverables along the way. And what they mean and how impactful they are, we have to frame very, very carefully, and that's clearly where we need the help of the community of people who really understand what's going on and with the strengths and the limitations.

I think the last point that is really tricky is how do we get from here to where we want to be, and that's the answer we don't have. Just as three years ago I

could not envision being where we are today, and I wouldn't be able to describe exactly what we already have, how we go from here to the national resource we want to have, that we need to have that has a sustainable business model, that has a shared infrastructure, that meets the needs not only of the Food and Drug Administration -- and that, obviously, is going to be our first priority -- but understanding that we do not in any way want to encourage duplicative activities. As we've said in the paper, there are -- health care information, it's a precious national resource, we don't want to waste it -- and we certainly don't want to waste the resources that are involved in understanding and analyzing and so forth.

We not only are short of financial resources, we operate on a very small budget, we are very short of experts to know how to do this, and as a nation we haven't quite yet figured how to rev up training those experts, so we cannot afford to be running parallel systems. So how we engage and make sure that the federal government is on the same page, that all the various activities are on the same page, that we're not querying data partners for the same information in six slightly different ways. How we get from here to there; how we influence the national dialogue is not entirely clear, but it is definitely through for such as these.

So Judy's going to spend substantially more time on this than I have on the specifics of what we've accomplished and where we're going, and Rich will follow with more detail. But I think we can sit back today and not rest on our laurels -- we have an enormous amount of work ahead of us -- but I think be very satisfied and, in fact, amazed that we have succeeded in developing an adverse, transparent, and accountable collaboration which I believe is precedent-setting. And I think others who've had (inaudible) can think about that. It took us a lot farther and invented a lot faster than

when we had thought.

As I said, we had an obvious, tangible threat such as a virus. And at meetings such as these and the various other activities that have been outlined by Mark in terms of having Brookings help march us along, we have to be vigilant to anything that can derail us. We have to be willing to course-correct whenever we need to and remembering that at the end of the day we are all here for the same reason, which is to better the health of this country, to the people in this country, and that we are inventing are we go a much more modern approach to doing that, although it will still be only one tool in our toolbox -- just like saying working with Harvard with snow proves snow -- Sentinel will never be alone, Sentinel finding, but it should help us very much modernize how we think about our therapies.

Thank you. (Applause)

DR. RACOOSIN: Good morning, everyone. I'm going to give you a little bit more detail about the activities that are comprising the Sentinel Initiative. Here we are two and a half years into the official program. I'll talk a little bit about the background and why we're here in the first place, talks in a little bit more detail about the pilot programs that you've already heard mentioned that have been underway for about a year and a half to help us actually pilot how we might conduct an active safety medical product safety surveillance. I'll revisit our convener activities on active medical product surveillance that you've heard described, but I'll put a little bit of FDA input into that and then wrap up by talking about the public-private partnership, OMOP, or Observational Medical Outcomes Partnership you've heard a little bit about today, also.

So just revisiting the FDA Amendments Act of 2007 for a moment, Section 905 is about -- talks about active postmark-at-risk identification and analysis.

And, specifically, it says that FDA should establish a postmark-at-risk identification and analysis system to link and analyze safety data from multiple sources, and it laid out specific goals for the number of patients that should be included in such a system. And that was 25 million people by last July and 100 million people by next July or a year from this July. And there's a little checkmark next to the 25 million because in July of last year we did meet and exceed that goal out through the Mini-Sentinel distributed database which you'll hear a little bit more about later.

Another component of Section 905 specifically said that FDA should be a utilizing data from a variety of sources including both federal health sources and private sector sources. And so two more checkmarks there as we have included out federal partners and our federal partner collaboration which I'll be speaking more about as well as the private sector in the Mini-Sentinel project.

Now in response to the FDA Amendments Act, a mandate to create this system for postmark-at-risk identification and analysis, FDA launched the Sentinel Initiative in May of 2008, and the goals of that program are listed on this slide. Specifically, one of the goals is to improve our capability to identify and evaluate safety issues in near real-time. So for those of you familiar with FDA, we have -- we have had for many years spontaneous reporting systems that capture reports that are either submitted to manufacturers who are then required to report them to FDA, or FDA can accept reports directly from health care providers and patients.

But these passive systems require FDA to await those reports coming in, and that can be a lengthy process as people experience potential problems, have to think about reporting them, report them to their practitioners, et cetera, and so we need a way of learning about safety issues more quickly, identifying them and evaluating them. So

that's one goal of this active surveillance system. The other is to enhance FDA's ability to evaluate safety issues that are not easily evaluated through the spontaneous reporting system.

So these are improving our access to special populations like children and the elderly expanding FDA's access to longer-term data which in some regard will likely require us to be able to link between databases in an anonymous way and, finally, expanding FDA's capability to look at adverse events that occur commonly in the population. The spontaneous reporting systems do quite well with rare, uncommon events that are often considered to be related to particular medical products. It's much harder to understand common adverse events like MI and fracture because generally they're not even reported to the database, and even if they are, we don't quite know what to do with them because they occur commonly in the background.

But by creating a system that has a defined denominator and has compared our groups, we can improve our capability of looking at these common events. And so I just want to reinforce that the active surveillance system that we're developing is intended to augment and not to replace the systems that we currently have in place.

So moving on to the pilot programs, I'm just going to briefly mention, highlight Mini-Sentinel because you're going to be hearing a lot more about it, but specifically this is the pilot that we have intended to develop the scientific operations needed for the Sentinel system and to create a coordinating system that has a capability of having access to relations with data partners to create a distributed system for us to pilot the evaluation of safety issues that are coming up from a variety of centers and from free market development things that are occurring in a post-market period. And this gives us an opportunity to evaluate how we might evaluate these safety issues in this

kind of distributed system, and we can come to understand what are the barriers, what are the challenges, and to really work on evolving the data infrastructures and the scientific methodologies that are needed to do this.

The federal partners' collaboration is our small distributed system with our federal partners, the centers for Medicare and Medicaid services, the VA health system and the Department of Defense. We are doing this project through interagency agreements, and the difference in this small distributed system is that we are not utilizing a common data model, and I don't -- I'm not sure that that phrase has been used today yet, but you'll be hearing more about it.

One of the approaches with a distributed system is that in order to run an analysis similarly across all of the data partners, each of the data partners transforms their data into a standardized format so that one analytic program can be run, and that's the model that's being used in Mini-Sentinel and that's the model that's being used in OMOP as well.

With our federal partners that is not part of the program; however, our approach has been to develop a common protocol, develop standard definitions for our exposures and outcomes as well as developing a common approach to the analytic methods and then for each of the data -- each of the federal partners to implement the protocol in their data setting, and this gives us an opportunity to understand how do we interpret data from the safety evaluations when we are not using a common data model, recognizing that we're trying, as part of the Sentinel Initiative and trying to understand a range of approaches to doing things, what are the challenges when you do one of these active surveillance evaluations without a common data model versus when you use a common data model which we're learning about from Mini-Sentinel and OMOP.

So that's the approach that we're using with our federal partners, and it's been a very productive collaboration, particularly because our federal partners, they have specific -- as they take care of their patient populations, they have specific safety questions that are important to them, that are important to FDA, and we can collaborate to better understand that and improve the care all around.

As you've heard today already, the Brookings Institution is leading our activities, our convener activities on active medical products surveillance, and this has really been an invaluable collaboration. It has allows FDA to access experts in the areas that are important to helping us develop an active surveillance system and the various topics of expert panels, the active -- the medical product surveillance roundtables. Some of them are listed on the slide, but it really has allowed us to access the expertise that we need as well as hearing about the latest projects that are going on in various -- the fine aspects of how do we do this.

So how do we think about linking data anonymously? What has been the experience of other projects that have tried to do active surveillance in their own settings in a state-based way and in other federal initiatives related to H1N1, what did that experience -- what were the lessons learned there that we can apply to Sentinel?

So this whole effort has been really tremendously helpful in gathering all of the expertise because, as you've heard today, we're getting, we've gotten where we're going or where we are today and where we're headed because of all of this collaboration and with all of the various smaller advances that groups are making. We can learn about them and in the active surveillance implementation meetings try to bring all of those bits of information together to think about how, ultimately, will we stand up the Sentinel system.

And finally, the public workshops like the one today. We really are appreciative to Brookings for helping us bring everyone together for these important discussions.

I'm going to finish by mentioning the Observational Medical Outcomes Partnership. Mark described this earlier. I just want to revisit it for a moment. It's a public-private partnership between the pharmaceutical industry, FDA, and the foundation for the NIH. And it's really been -- it's a research effort focused on developing methods for use in observational data for active surveillance. The goals have been to conduct this methodologic research as well as developing open-source tools and capabilities and really establishing a community around research in this area.

As Rachel mentioned, we are in need of more people moving into the area of development and conduct of active surveillance, and a project like OMOP is important in creating this research community to move this forward. If there are graduate students out there in the crowd, come work with us because we can use your help.

I'd encourage you to go to the website because a tremendous amount of materials that OMOP has developed in the area of methods development and data characterization tools are there as well as the description of the common data model and the other work that's been done. As was mentioned yesterday was the OMOP symposium where the results of the main OMOP methods experiment that were conducted through the first two years of the project were presented, and clearly tremendous progress has been made and beginning to understand the methods landscape. But there's a lot more work to be done, and, fortunately, OMOP will be continuing for another year.

So I think you've probably gotten the sense that this is a long-term,

complex initiative, and we're really -- we are implementing it in stages as the scientific methodologies and the data infrastructure evolves. We are
-- it's of utmost importance to us to maintain the privacy and security within the distributed system, and you'll hear more about the privacy panel that has been part of Mini-Sentinel that has helped develop the policies in that area. And we are here because we want to hear from all of our stakeholders so we can continue to address concerns that may come up as we move this program forward.

And, finally, we are really interested in trying to address how the eventual Sentinel system can function as a national resource, as has been mentioned, and really complement other federal initiatives that are using distributed systems. So we know within the HHS immediate office and within ARC there are projects going on to use distributed systems for comparative effectiveness research and product quality initiatives. And we want to make sure that we can move this effort forward in as collaborative a way as possible so that, as Rachel mentioned, we're not making duplicative efforts, and we can use our resources together to move all of our initiatives forward.

Thank you. (Applause)

DR. McCLELLAN: Thanks, Judy. Thanks, Rachel. Just again, warning you about the discussion from here, Rachel and Judy are going to participate in a discussion after the first panel where we're going to try to get into more depth about a range of issues around Sentinel implementation to date, and some of these issues going forward. So I want to hold any sort of big substantive questions until then. But I did want to check right now, does anybody have any clarifying questions about Mini-Sentinel, or about anything else you've heard so far?
We'll hold off on the substance, just any sort of clarifying technical questions?

Okay, that's going to be a pretty good discussion in a little while, so thank you all for coming up now. They will be back in a little bit after we hear from the remainder of this first panel. And I'd like to ask all of our first panelists to come up while I introduce them. This set of a group of Mini-Sentinel investigators who are going to provide an update on the pilot's development and future plans. And again, we're going to have an extensive discussion here so that we weren't going too long without a break. What we're going to do is hear from all four of them and then take a short break and reconvene for really an hour of discussion with Rachel and Judy as well about all of these issues related to Mini-Sentinel.

But right now I'm looking forward to hearing their opening comments, and let me introduce very briefly Rich Platt, the professor and chair of the Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute. Rich is the PI on the contract with the FDA to develop Mini-Sentinel. As I mentioned earlier, this includes a very large and diverse set of organizations.

Next, Lesley Curtis is an associate professor of medicine at the Center for Clinical and Genetic Economics at Duke University School of Medicine.

Next is Kristen Rosati, a partner at Coopersmith Schermer & Brockelman, PLC. Thanks for making it here today, Kristen.

And also Bruce Fireman, who's a biostatistician and research scientist at the Division of Research at Kaiser Permanente in Northern California, who will talk about they have been involved in Mini-Sentinel to date and will give you some, I think, a good set of perspectives on where Mini-Sentinel is and what's coming up.

So, Rich, let me turn this over to you.

DR. PLATT: You know, being the principal investigator usually means

you're the guy who gets all the complaints, and I have to say this is an extraordinary activity because I'm probably the person who is having the most fun in this activity.

I tried to make a slide showing the names of the people who have been actively engaged among the 27 partner organizations involved, and it turns out that the fund size is really too small to do that. But I'll say that the things that the four of us are going to talk about involve the substantive involvement of about 150 people who are engaged in a meaningful way in creating the things that we're talking about. And that's only on the contractors' side. There is also a large number of people at FDA who have been very active participants in making this work.

So there isn't time to name names, but I will say that Rachel and Judy and Moe Serrob have been as good a set of federal partners as I've encountered in what's getting to be a long career of working with federal agencies. So this is really not only an activity that is successful as it goes, but it's also one that's quite a positive experience.

This is a slide that Janet Woodcock used just over a year ago in which she laid out the things that FDA was expecting of the Mini-Sentinel program. There's a lot of words here, so let me boil it down to say that our marching orders were to do seven things: one, create a coordinating center; second, to build a distributed data system; the third was to engage three or more health data environments; the fourth is to create a system of governance that would sustain this activity; the fifth was to build a secure communications facility; the sixth was to develop epidemiologic and statistical methods to the extent that they're needed to make this work; and then to do, to evaluate topics that FDA identified for us as being important ones.

So let me give you a progress report on how we're doing in a year later.

We've stood up a coordinating center that has an operations center in Boston and a planning board that is distributed, has membership from all over the partner organizations and others, including a patient representative. And I'll mention it particularly that a project operations committee has done yeomen work in creating policies and principles for us, and our privacy panel has provided terrific guidance for us.

We organize our work according to data methods and protocol core, and each of those has work groups that are stood up and do work on specific topics as needed. So those are sort of ad hoc organizations groups that do the real work of the Mini-Sentinel.

The governance policies that we've developed so far focus on seven areas. I've listed them here but I'm going to highlight the first three. The first was the decision by FDA to consider the work that we're doing to the part of FDA's public health practice rather than research. And it's a decision that followed a substantial amount of thought and consultation and work and that has very important implications -- partly they're operational implications -- for what it takes to do work. But, more importantly, I think in really firmly establishing the kind of activities that the Mini-Sentinel's engaged in as an activity that is addressing an important public health priority rather than simply generating new knowledge.

The second thing that we have spent a lot of time on is the sort of the theoretical underpinnings of the distributed data system, and that is the principle of having as little of protected health information leave its existing home as possible. And so articulating that in a way that is flexible enough so that data can move when it has to, but doesn't move when it doesn't have to was also important work.

And the third policy is the fact that everything we're doing is work that we

expect to appear in the public space in a timely way. One of the unusual -- one of the surprising things about our initial interactions with FDA was the fact that not only did we have to not have to negotiate for the right to publish our findings, and that is sometimes an issue in the work that we do with federal agencies, but we actually had to have a conversation about whether it would be possible to hold off on making certain things public so that we could publish them in the peer view literature. And it's a first for us.

Kristen will talk about the work that the privacy panel has done in thinking through and articulating principles on privacy. There's a whitepaper that I'm sure she'll refer to that's available on our website. This is back to 2010. We were hoping to be able to make available administrative and claims data for 60 million people and listing the other things here. We spent all of this year working on the administrative and claims side since we had to start somewhere, and that's the largest amount of data.

In fact, Lesley will show you that we now have data on 71 million people. We think those are -- when Mark talks about queriable data, those are the data that are queriable for FDA. These are our distributed data partners. We were supposed to have data from three. In fact, the data, the 71 million come from 15 organizations that are part of Wellpoint, Kaiser, Humana, HMO research network. Aetna is joining the Mini-Sentinel team. Vanderbilt will also be data provider. There are also partners that are not data partners but bring content expertise, and I've listed them here.

Mark's already showed you the distributed analysis framework that we use. I'll only point out that part of the special sauce is the Mini-Sentinel portal which uses software that we've developed over the past several years using support from AHRQ which has staked out the space distributed analysis and has allows us to make progress much more quickly than we otherwise would have. This is a team that Jeff Brown has led

that's built and made operational this portal.

We have secure communications facilities, FISMA compliant file transfer capability. We also have a public website, minisentinel.org, where most of the things that we're talking about either are now or will be available fairly soon. So I invite you to come visit the website. The kinds of things that are on it are we'll put the results of our completed evaluations. We have information about every one of the ongoing evaluations that has been sort of formally approved. Our methods, tools, policies, procedures, protocols, computer programs, will all be -- the ones that are finished enough to show are there.

We've put a substantial amount of work into data, into methods development. We're not going to be able to spend time this morning saying much about the methods develops that we've been doing, but that has been both epidemiologic methods development, developing a taxonomy of study designs that might be used for different kinds of questions that FDA is interested in and different kinds of data resources that are available.

We also have been doing some work in getting the best understanding that we can of the existing knowledge about how to use electronic data, and we've been doing a substantial amount of work in novel statistical development to address some of the major gaps that we know we're going to have to deal with in order to make the best use of these data.

So back to Janet's slide, I'd say we've done -- we've done pretty well on six of the seven things that she gave us to do. So as the 2003 Red Sox would have said, it's time to cowboy up and actually do some safety evaluation. So that's the work of this coming year, actually learn something that will be useful for clinicians and for patients.

Bruce is going to describe the protocol that we will be launching fairly soon to evaluate acute myocardial infarction in relations to orohypoglycemic agents, but we'll also be working with FDA to evaluate safety issues, new safety issues for drugs that have been on the market for awhile and to evaluate the impact of FDA's regulatory decisions on the use and health outcomes of products that are the targets of those decisions.

We're also -- we're also going to be working with the Center for Biologics on, now on assessment of effects on some vaccine safety issues. There's a prism project that Judy mentioned which was an ad hoc evaluation of H1N1 vaccine safety is now formally part of the Mini-Sentinel program, and we are delighted.

Last year I thought that our situation was like this: engaged in a good line of work and enjoying the things that came down the pike. I'd say this year we're realizing that we're really dealing with heavy machinery and there are a lot of moving parts. So let's -- that doesn't look like Lesley there, but running the data core is not a job for people who don't know how to stay out of harm's way.

Last year I listed these eight challenges as being things that we needed to be mindful of, and this year I'd say it's the same eight challenges and the same two that are at the top of the list: That is, on the one hand we appreciate that it is important to have the capacity for timely evaluation of the data that are available because it's important to now that products are safe if they're safe, and it's important to know they're unsafe if they are unsafe.

On the other hand, we recognize the tension and the importance of avoiding false alarms that can have an enormous negative impact. And so building the infrastructure and the capability of doing these studies is an important piece of work, but

the leitmotif that governs all of this is making sure that we achieve the right balance of speed and care, and that we avoid saying things that are really misleading.

So I've already shown you that minisentinel.org is a living, breathing website, but one day while I was thinking about something else I typed in minisentinal.com, and you actually get someplace. And I'll just point out that I don't know who owns minisentinal.com, but you can buy it. So if you take a market-driven view of the world and ask how are we doing, I'd say a URL that you could buy for max $15 last year now appears to have a market value of $2,000, which is a return of investment that's pretty good, so.

SPEAKER: You'd better buy it now.

DR. PLATT: Right. So we have yet to do the most important work that Mini-Sentinel has to do. On the other hand, we are delighted to have made as much progress as we have, and looking forward to continued -- continued work here.

Thank you. (Applause)

DR. CURTIS: It's great to be here today to share with you some of the accomplishments of the data core over the last year. Really, I believe over the last year we've created a really productive and actually quite fun collaboration among different data environments, institutions, and we've built an exciting and I think unique resource as well.

Today what I'll do is talk about the process that we used to create the Mini-Sentinel common data model and how we actually developed the distributed database. I'll also touch on the core infrastructure that's been built -- Rachel alluded to this a little bit just a minute ago -- and then talk about how we'll be generating useful information for FDA.

So a common data model, as Judy mentioned, is essentially a commonly defined data structure with specific data definitions to accompany that so that all partners or all institutions in the distributed environment can transform their data in a similar really identical way. In creating the Mini-Sentinel common data model, we began by developing some kind of ground rules or guiding principles for the work that we would do. We did a careful review of existing data models, and then we went through a fairly detailed process of revising and revising and revising draft data specifications.

Now, when I talk about laying the groundwork, we really did do that by creating these kind of common understandings, guiding principles that we would use throughout our work together. There are 11 guiding principles in all. I've highlighted three here that I think really are both broadly stated and I think nicely articulate the kind of underpinnings of the work that we're doing.

Simply put -- you could read them here, but simply put we value the data partners and the expertise and experience that they bring to the table. We are committed to creating a distributed database and environment that is really quite efficient. And, finally, we're committed to creating a distributed database that meets the needs that it's supposed to meet but is also flexible and able to develop over time.

We did a fairly thorough review of existing common data models because we didn't feel the need to reinvent the wheel, and we certainly didn't want to make mistakes that had already been made before, or we wanted to learn from everyone else. Included in that review were some of the data models that you've heard about today -- prism, OMOP, the HMORNs, virtual data warehouse, the vaccine safety data link and several others, and from that review several kinds of lessons or themes emerged.

First, we were reminded again and again that it is feasible for many data

partners to assemble these patient-level files according to some common data specifications. And while doing that they can also retain complete control over the use of their data. As you've heard already, that's really, really an important point, but while they do that they can still work toward common objectives.

We were also reminded that coding varies by data partners' coding schemes that are used to vary, and it's really important to understand those differences and again to keep those data partners and the people who truly understand those differences best at the table for ongoing dialogue.

And, finally, we concluded at the end that all of the analytical imperatives that have been given to us could be met using this distributed approach.

So, as with any development process, we began with a good old straw man, the common data model that really required what we thought would be minimal transformation so that we'd maintain the granularity of the source data and also leverage this prior experience. We spent a fair bit of time reviewing and talking to data partners about their experiences with other common data models and wanted to make sure that we put that experience to good use.

With each iteration of the common data model we engaged the data partners in a discussion about that data model that we had share with them, and questions like: Can you implement this? Are these definitions? Are the tables, do they include -- are they specific enough? Are we specific enough in our direction to you so that you can transform source data in a common way? What are we missing? And are these requirements consistent with what you expect? And, of course, this is a partnership, and so this process actively engaged and involved FDA along the way as well.

Version 1 of the common data model, as Rich said, rests on administrative and claims data and has five major data areas. There's an enrollment table. We include information about demographics, outpatient pharmacy dispensing, utilization, and mortality. Now, although all of these data partners had some experience with common data models, the work of transforming this initial transformation was really a major undertaking for everyone. Each data partner translated its local source data to this common structure and in the process documented exactly how they had done that. So data element by data element, table by table, telling us how source data were transformed into this common data model.

As with everything that I've talked about today, the work took place through a series of weekly conference calls, countless e-mail exchanges, and many, many, many one-on-one conversations. Then the transformed data were characterized using some standard programs that the operation center had developed. Now, I want to reiterate that at all times these data remained behind institutional firewalls, so we used this distributed approach that's already been described to gather information and to characterize these data.

Overall, the Mini-Sentinel distributed database spans from 2000 to 2010. Different data partners have data going back to, you know, different beginning dates. Collectively, there are more than -- nearly 120 million records in the enrollment table the vast majority of which have both medical and drug coverage. There are more than 70 million unique members included in the enrollment tables, and of those 22 million were current as of January 2009 with both medical and drug coverage. This amounts to about 170 million person years of observation time with an average per person observation time of about 28 months.

Slightly more than 50 percent of the enrollees are female and about two-thirds are between the ages of 20 and 65. That's about 45 million people, so for reference the young -- the youngest group here from 0 to 52 weeks, for example, there's about 230,000 people, and the very oldest group, the 85+ group, as about 3 million enrollees there.

The operation center has done a tremendous amount of work over the last year building the core infrastructure that supports this distributed system. I mentioned the standard programs that had been developed to characterize the data. A library of programs also exists to check the quality of the data that are being created or that have been transformed.

We also undertook a formal assessment of the data partners' technical environments which really expanded beyond just technical issues to really try to identify barriers, opportunities, and even non-technical issues that might come into play. With the first transformation complete, preparation is underway now for the beginning of quarterly refresh cycles to the Mini-Sentinel distributed database and, along with that, an empirical assessment of data latency. And, as Rich mentioned, the secure web portal for distributed analyses is a huge accomplishment.

So to return to this picture one more time, just to sort of reiterate how the pieces fit together and what the data core as done and what the data partners have done, local data have been transformed into -- or source data have been transformed into these local data sets that you see described here. The infrastructure is in place now to begin the querying of these data, and we've also developed, I believe really importantly, an approach to not only -- not only fields the kinds of queries that will be necessary for a full-blown surveillance program like the one that Bruce Fireman will be talking about later this

morning, but also to respond to the kind of rapid questions, rapid queries that come up as questions arise.

To do this Jeff and his group have created really a library that will continue to evolve of modular programs that can answer sort of specific and common feasibility type questions. I've listed them here, and you'll see that they really will be quite useful for those kind of quick questions that arise. So the first looks at drug exposures for a specific period, how many exposures were there over this time period to a given drug?

This second expands that a little better, actually narrows that a little bit by saying tell us about drug exposures among enrollees with a specific condition.

The third begins to put together exposures with outcomes in a very simple way summarizing those results across the partners.

And then the fourth explores and summarizes concomitant exposure to multiple drugs. We're very excited about the progress that's been made but certainly understand that a lot of work lies ahead. And thanks again for the opportunity to share with you what we've done. (Applause)

MS. ROSATI: Well, good morning. It's really a pleasure to be here. I'm Kristen Rosati from the law firm of Coppersmith, Schermer & Brockelman. I am in Phoenix, and it's really been a pleasure being involved in this project. I do a lot of work across the country in using electronic help information for research and public health and other purposes that aren't directly related to the treatment of patients. And this is by far one of the most exciting projects I see happening across the country because there's a real chance and a likelihood that there'll be real impact on the health of Americans.

So the FDA and the Mini-Sentinel folks are building this incredible public resource using electronic health information, and one of the really important things that

I've seen is that the FDA and the Mini-Sentinel project personnel are incredibly committed to the privacy of that health information. And I think this is essential to build public trust in what the FDA is building here. I think the public really supports the use of health information as long as it's kept in a secure private way for purposes such as research and public health activities that will increase the health of the public. So I've been very pleased to see the real sincere commitment to privacy in the project team.

As you'll see and as you've already seen the architecture of the Mini-Sentinel project itself really is committed to privacy because it's a distributed data network, as I'll talk about, complies with federal law and, more importantly, it goes beyond legal compliance, and the Mini-Sentinel project team has adopted policies that reflect what are called "fair information practices," which is really the bedrock of a lot of federal and state laws and good privacy practices about how to use health information.

I've had the pleasure of working with two incredibly smart people on the privacy panel for the Mini-Sentinel effort. One is Deven McGraw, who's the director of the Health Privacy Project of the Center for Democracy and Technology. I know Deven's here, raise your hand, we have to point you out. Deven's really a committed advocate for consumer interests, not just the interest in patient privacy which, of course, is essential to what we're doing here, but also consumer interests in building these resources so that we can leverage these wonderful electronic health information resources we're building across the United States.

And also, Barbara Evans, who's an associate professor at the University of Houston, who has really brought an important perspective to the privacy panel. And we've been working together on evaluating the legal compliance for the Mini-Sentinel network and also helping build the privacy policies to reflect those fair information

practices.

Now, you've seen this before, obviously. If there's one thing you're going to get out of today's conference is that you will understand that the Mini-Sentinel is a distributed analysis -- distributed network. And that's really the key to great privacy protection because the individually identifiable information, which is really what consumers and patients are concerned about protecting, stays behind the firewalls of the data partners. And so a distributed data network used for analysis, whether it's for these public health activities or for research perhaps in the future, really protects individual patient privacy because the data source hold onto that individually identifiable data.

So they maintain the physical and operational control over that source data. The put it into that common data model so that you can do good analysis over many different points of data sources. The operation center or the FDA send standardized queries into the data partners; the data partners scan it against their data -- you can tell I'm not a bioinformatician, but I'm perhaps talking in a way that the consumers can understand -- and then the data partners execute those queries against their data and then share summary results back to the operation center.

Occasionally, that summary of the summary results aren't sufficient to do the analysis, so the data partners may occasionally be asked to provide patient-level data to the operation center to do a good discrete analysis of a particular drug safety event where the data partners strip all of the individually identifiable information out of that patient-level data before sending it to the operation center or the FDA. So that's really key to continuing to protect patient information even when that patient-level data may be necessary to do a more particular analysis.

Now, occasionally, the data partners who are doing the analysis with

their common data model may not have the original source data. Health plans, for instance, are working from their health claims databases, and occasionally it may be necessary to ask for a patient medical record from the original source data to confirm a drug safety signal, for instance to evaluate when a particular drug was prescribed or administered to an individual, whether there's any other clinical indications for that patient that would count against that drug causing the actual problem.

In those circumstances, the data partners may ask for individual information from the data sources, but the important thing there is they only ask for what they need -- that's called a "minimum necessary standard" under HIPAA -- and they only use that information for an analyzing the drug safety event, and that data is never used for any other purpose. So the policies that have been adopted for Mini-Sentinel, even when individual information is required to do the analysis, are very respectful of the patient privacy.

From a legal compliance perspective, HIPAA is the primary source of what we look at when analyzing the use of protected health information. And HIPAA permits the use and disclosure of health information, even individually identifiable information, for public health activities and to a public health authority. FDA itself, obviously, is a public health authority, but public health authorities can also include others that are contracted with the FDA to do an analysis for the FDA. So the operation center for Mini-Sentinel as well as the subcontractors that contract with the operation center are all treated as public health authorities for HIPAA compliance purposes.

As Richard mentioned, these activities are public health activities, public health practice and not research, so the approval by an institutional review board is not necessary which is important for making sure that this analysis is a streamlined process

when you're thinking about all the different data sources that we'll need to touch as Sentinel gets off the ground and develops further.

Now, there are a couple of other sources of law that data sources always have to think about when participating in any of the public health activities or research. One of them is what are called the Part 2 Regulations, which are the federal substance abuse treatment regulations. It's unlikely that these will be affected by Sentinel because that sort of regulation just protects information that identifies someone as a substance abuser, and because only data is presented in summary format that is not individually identifiable, it's very unlikely that those regulations will be triggered.

State confidentiality laws also play a part. There's a plethora of laws out there that data sources have to deal with, so each one will have to analyze their own state laws to make sure that there's no additional barriers to participating in the Sentinel Initiative and the Mini-Sentinel: things like genetic testing laws, mental health laws, communicable disease and HIV protection laws. But most state laws -- and this is just a general statement -- but permit disclosure of health information for public health activities. Most state legislatures realize that there's very important public purposes in addition to protection of patient privacy. So in large part, state laws will not be barrier to others or to the data sources participating in Sentinel I either.

But going beyond legal compliance, I had mentioned that Sentinel and the Mini-Sentinel project has adopted policies that reflect fair information practices which go beyond what the basic baseline is required, by HIPAA for instance: things like ensuring data integrity and quality, collection and use limitation. So data is only collected for a particular purpose and only that amount of information necessary for the purposes collected.

And the consumer participation, openness and transparency, the FDA has been fabulous at making this process very transparent to the public and to consumer and to involving them in the decisions about how health information is appropriately used. Security safeguards and controls and accountability and oversight are essential.

Now, here's just kind of a quick recap of what those Mini-Sentinel privacy policies reflect: The keys here are that consumers and patients are not identified in any information sent to the operation center or the FDA. So again the individually identifiable information stays at the data source.

Second, any information collected for Sentinel purposes, whether it's identifiable or not, is only used for Sentinel purposes, so it is that collection and use limitation principle that is so essential to fair information practices.

And, finally, the information is secure. Those are really the bedrock principles that are reflected throughout the policies for the Mini-Sentinel project.

So as a privacy attorney looking at how this has been structured, I think the public should be absolutely assured that the FDA and the Mini-Sentinel contractors are committed to making sure that the system is structured and the policies are pursued in a way that really respects individual privacy and really makes respectful use of the health information that is so important to make this project work.

Now, thank you very much. I look forward to your questions in a moment. (Applause)

MR. FIREMAN: Well, good morning, everybody. This is going to be an overview of our plans for surveillance of acute myocardial infarction in users of anti-diabetes drugs. These plans have come out of a very collaborative and deliberative process that's had lots of input from a large number of researchers at the data partners,

at academic institutions, at FDA. And it's been an enjoyable process, but a careful and deliberative one. The write-up of our protocol and our deliberations is available on the website that Rich mentioned, and I invite you all to get more than this over, you know, more details there, the write-up that was led by Joe Selby, a diabetes researcher at Kaiser Permanente.

Our aims are to develop and assess a framework and infrastructure for monitoring drug safety in large populations using, as you've heard over and over again, distributed databases. And for this pilot effort we're going to be monitoring acute myocardial infarction in users of anti-diabetes drugs and, more specifically, we're examining the association of heart attack risk with saxagliptin, a recently-approved DPP-4 inhibitor used for treatment of diabetes.

And as Rachel mentioned earlier, a big advantage of looking at high-tech risk in saxagliptin users is that there's going to be a randomized trial, and as we're -- of CVD risk in saxagliptin users, and so as we're developing and testing and evaluating our methods and our data and our infrastructure, hopefully we'll have results from this trial to compare with.

We have a big population with type 2 diabetes that we're going to be examining. We're focusing on adults who have had a diabetes diagnosis and an oral anti-diabetes drug during a 12-month baseline period. That's who we're going to be doing surveillance on to see whether they meet our entry criteria. They have to have been member for 12 continuous months in a health plan associated with one of our data partners.

There is going to be very few exclusions from our study population. This is a broad population-based study. We will be excluding patients with type 1 diabetes

and excluding patients under 18 and patients who have been taking only insulin because they're likely to have type 1 diabetes. And we're also excluding people who have had a recent heart attack within 30 days of starting one of our study drugs because their risk of an adverse event is extremely high and very hard to quantify and adjust for as we're making comparisons across our study drugs.

The study period we'll be looking -- we'll be doing active surveillance on goes from July in 2009 when saxagliptin was licensed through June of 2013. We'll be looking at baseline data going back further, though, you know, for adjusting our comparisons we'll be going back a few years. And all of our data partners, as you saw earlier, have data that permit that.

In our study population now are 1.3 million patients with type 2 diabetes, and over this study period we'll be accumulating 5.2 million person-years that we're going to be monitoring for AMI. And given our baseline rate of about nine heart attacks per thousand person-years of follow-up, we expect about 47,000 heart attacks in this study period during this period of active surveillance.

So we're going to focus on a comparison of new users of saxagliptin with new users of -- for comparative drugs. And these are the comparators: saxagliptin, pioglitazone, sufonylurea, and long-acting insulin. Follow-up is going to begin at the first prescription for one of these study drugs and end when the user quits or switches drugs or leaves the health plan.

I want to -- this new-user cohort design has a lot of strengths because the baseline period and starting follow-up at new use permits the comparisons to be balanced and adjusted for possible differences between the users of the different study drugs with respective possible confounders. By restricting to the new users it means that

we're not going to be making inference on the drug, heart attach association either from prevalent users of these study drugs, or from within person on/off changes. People go on and off and switch drugs, and we'll be investigating some of these methods in other settings but not in this, in these plans that I'm discussing here. And that's because we feel we can address possible biases from unmeasured confounders and from measured confounders better in, when with a new user design.

Our primary outcome, as I mentioned, is heart attack. It's a good place for us to be starting because this is a very important event that's of great interest to the public and is well identified in our databases with numerous studies, at Kaiser Permanente and elsewhere, have shown very high positive, predictive value for heart attacks identified by these means and these databases.

Our secondary outcome is the broader classification of acute coronary syndrome. I want to mention that we have two main measures of our outcome which we'll be following over time, and by "time," I mean time on study drug as well as calendar time. And they are the relative risk and risk difference that might be associated with one study drug versus the other. One's a little more tractable and, in many of our statistical models, the -- and more reliably measured -- the relative risk; the other is important for weighing the harms and benefits, and they're closely related.

We're going to be adjusting for a number of possible confounders including prior cardiovascular disease, comorbid conditions, patient demographics, other drugs that patients are using, the history of patterns of use of health services. And we're going to pay very careful attention to adjustment for differences in our practice settings and data, data management for in code -- possible coding differences by looking carefully at differences by site and health plan, and also differences over time. That's time-over on

drug as well as calendar time.

We're going to be considering several adjustment strategies in methods. As I mentioned before, we're going to be restricting our comparisons to new users. We're going to be stratifying carefully for prior cardiovascular disease. We're also going to be stratifying by site, and we're going to be adjusting by covariant adjustment for these other factors that I outline above.

We're going to be testing and evaluating and using gaining experience with several alternative methods of adjusting for these possible confounders, and which we're adapting to this distributed data environment that you've heard a lot about today because we're not dumping and pooling all of the data together. So we're going to be looking at the propensity scores and disease risk scores and weighing some of their advantages. Both of these we've developed some methods for using them in the pool of data with making -- there's a number of advantages and disadvantages which I see here.

Since I only have a minute, you all can -- we can -- of each of these which I could talk about later -- I want to emphasize that this is sequential surveillance. It's ongoing. We're going to be looking -- our first analysis is planned in a couple of months, and that will include all of the experience in this, and our data partners that's been accumulating since the licensure of saxagliptin. We plan nine coordinated analyses of the accumulating data with the final analysis in June of 2013. We're going to be using sequential statistics that are adjusted for multiple looks. Each look is going to include all of the data, but we're going to be paying careful attention to the multiplicity issue.

I want to say that -- a few remarks about the size of the relative risk that we're going to be able to detect or rule out. And assuming that we accumulate 23,000 person years in saxagliptin users and a similar amount in matched users of a comparator,

and expecting about 9 heart attacks per 1,000 person years, then we're going to have about 80 percent power to detect a relative risk of 1.3, which is quite as bit of power.

And I have signals don't arise the confidence intervals that we're going to be estimating will be informative about the size of the relative risk and risk difference that can be ruled out, and the amount of reassurance that's appropriate, given that we've been looking and haven't seen anything.

And this surveillance is designed to be worthwhile even if saxagliptin isn't used much because comparisons of heart attack risk in the users of any diabetes drugs can yield worthwhile reassurance or safety signals and lessons about statistical methods, and evidence about the value of Sentinel's data and infrastructure regardless of saxagliptin uptake.

And so in summary, this overview is just let me know that Mini-Sentinel has developed plans to examine heart attack risk in saxagliptin users versus users of four comparator drugs. We're going to be assessing the feasibility and value of heart attack surveillance in users of anti-diabetes drugs using the distributed databases, and we're going to be evaluating methods for monitoring drug safety in these large dynamic populations.

Thanks very much. (Applause)

DR. McCLELLAN: Thanks very much for all of the presentations.

I want you to hold your questions, or rather use the next few minutes to think of some really tough questions for all of the panelists.

We're going to take a short break now. I'd like to keep it to about 10 minutes or so to just stretch your legs and so forth. And we are going to be breaking for lunch after this panel discussion. Then we're going to reconvene in here with these four

panelists plus our FDA leaders to discuss Mini-Sentinel.

One other thing for those of you who are in the overflow room, there are some additional seats in this room, and we will definitely try to make room for you if you'd rather sit over here. So see you all in about 10 minutes.

(Recess)

DR. McCLELLAN: Everyone please head back to seats so we can get started.

All right, we're about ready to start. I know this was a short break. We do have lunch coming up soon, but I wanted to make sure we had plenty of time for discussion. Now, you all have gotten a lot of information this morning on all of the progress and the Mini-Sentinel Initiative and how it fits into the larger strategic goals and implementation framework that FDA is trying to implement. So, all of that on the table now for discussion.

Before opening up to comments I just wanted to check with Rachel Behrman to see if she had any additional perspectives or comments after hearing from the Mini-Sentinel presentations, anything else to add or clarify.

DR. BEHRMAN: I guess two points. Should I speak to the diagram in question or --

DR. McCLELLAN: Go ahead and talk about --

DR. BEHRMAN: Apparently there was some concern expressed of whether diagrammatically -- and we have struggled mightily with diagrams over the years -- whether diagrammatically it's just the FDA has direct access to patient medical data, which we do not -- that's point one -- at least through Mini-Sentinel. I'll keep on our attorney, who's here, who has been instrumental in helping us articulate this clearly under

a public (inaudible) authority, sometimes we do have to go out and seek patient-level information. But that's no different than what we do now.

I thought that the overview this morning was a pretty excellent demonstration of again what has been accomplished. And to paraphrase something Rich wrote about a year ago that we we've turned, and again through this collaboration, through hard work and a lot of careful thinking, we've turned, quote -- or paraphrasing, a few words in the FDA Amendments Act into a vibrant, productive program that's actually producing information. I think to do so in a short period of time really speaks to the commitment of everyone involved, and on behalf of the agency I'd like again -- once again, just like to thank everyone for that commitment.

DR. McCLELLAN: Thank you. Let me remind people that there are microphones in the back of the room. It would be great if you have a question that you could go there to ask, and I want to -- and get -- encourage anyone who's sitting in the overflow room to participate as well. So, please feel free to start with the questions right now.

DR. RACOOSIN: Mark, could --

DR. McCLELLAN: Yes --

DR. RACOOSIN: Could I just --

DR. McCLELLAN: Judy, you had a clarification first. Go right ahead.

DR. RACOOSIN: I just wanted to respond to the -- one of the presentations this morning.

You heard about the detailed plans for the evaluation of saxagliptin and kudamie and the comparison to the other diabetes drugs. I think a tremendous amount of work went into planning that protocol, and I think it raises one of the issues that we'll

be continuing to grapple with, which is how do we scale up, if you will, because there are many questions that we have. You know, with every newly approved medical product, there are safety questions that we're going to want to evaluate, as well as questions that crop up, you know, periodically during the marketing of a product. And so I think that's something that we will be focused a lot on in the coming year -- is to think about, you know, from what we've gone through with that first process of planning a protocol for an active surveillance evaluation: How can we streamline the process for developing additional protocols as we want to expand, you know, to look at more questions.

The modular programs that Lesley mentioned at the end of her presentation are going to be key, because they are programs that are ready to fit in the various bits of information that we need to -- that would help us to narrow it to the specific question, and I think the process we're going to be thinking about is, you know, how to go from the modular programs to the more complex analyses, making sure that we have -- get useful and actionable information out of those evaluations.

DR. McCLELLAN: Okay, Rachel?

DR. BEHRMAN: And just to expand on that, in addition to being able to be scalable and timely and nimble and respond to urgencies and emergencies, this also speaks to the strength, the fact that this was not developed in isolation but we really took advantage of all available national expertise.

One piece we alluded to this morning and haven't explicitly said, so I'll put it on the table, is how to better, more effectively involve regulated industry in those discussions. But they're obviously a key stakeholder, and there are some complexities involved, and the governing system certainly at the moment fully -- as it is fully financed or -- so financed -- the level its financed by the Food and Drug Administration raises

some questions about how we are going to incorporate, if you will, industry studies. But I think as part of the national research, that's something we're going to have to grapple with and solve.

DR. McCLELLAN: Mm-hmm, and that's a good topic for further discussion. I wonder if any of the panelists had any further comments that they'd like to make, again kind of sticking with the topic of the saxagliptin protocol -- how that was developed, kind of lessons or implications for doing this in future applications of the Mini-Sentinel or the Sentinel system?

MR. FIREMAN: Well, it was an enjoyable collaborative, deliberative process, and so we had -- my input from a lot of top people -- as I said, I think the issue that was raised about choosing comparators was an interesting one. We wanted to be able to make inference about what would have happened to saxagliptin users had they been taking something else. But there are a lot of alternatives that are out there in clinical practice. And we think that something can be learned from each of them, so we -- after a lot of deliberation, we started out with a couple of comparisons. We expanded to four. And we think -- the reasoning and deliberation that went into that I think was helpful, and our deliberations are, as I said, are, you know, summarized in a useful document that's available on the website that Rich put up there.

All of the issues in terms of validating the data, adjustment for confounders, doing appropriate statistics as we look at accumulating data over time during the surveillance period, interpreting the data and not just when we're detecting signals but how much reassurance is appropriate when we don't detect signals, how much reassurance can be derived from the statements about how big of a signal we want to notice; and, you know, had there been something out there. So, I think we put a lot of

thought into it but there's a lot more left to learn.

DR. PLATT: So, I take -- there are two ways Mini-Sentinel will make progress. One is by taking what we've learned directly from the development of this protocol and applying it to other questions of interest to FDA. So, given the investment, it's well over a thousand hours of thoughtful clinician/epidemiologist/data partner time. It will take a lot less work to build the next protocol that looks for myocardial infarction in relation to any other therapeutic agent. And similarly, we've thought through a lot of the issues around studying the outcomes of diabetes therapy. So, if you ask where would the quick winds be next in terms of scaling up, it would be to start to expend what this process has learned to those kinds of settings, and there may be important ones for FDA to consider, whereas it'll be a lot of sitting around the table and thinking again when FDA has an interest in studying pancreatitis as an outcome or acute liver injury, because those will all take a similar kind of convening of FDA experts and clinicians and epidemiologists with data experts. So, some of this can go fast, and some of it will be a hard slog.

DR. McCLELLAN: Thanks. Further questions?

MR. MINES: Yes, thanks. I'm Dan Mines from HealthCore in Wilmington, Delaware. Thanks for a really nice presentation.

My question has to do with the saxagliptin study, and I'm trying to place it in terms of the categories I had in mind in terms of evaluating drug safety questions. Traditionally we think about signal detection, maybe signal strengthening studies, and then full-blown hypothesis testing studies. As I heard this study described, it sounds to me a lot like a full-blown pharmaco(epi) prospective cohort study with preplanned interim analyses. Is this what we mean by active surveillance?

DR. PLATT: I'd say the boundary between sort of signal refinement and

full-blown epi studies is a fuzzy one. But our take is that we're in an environment where FDA has reason to want us to evaluate a specific outcome of an exposure, and that takes us from signal discovery into the refinement area, and we're specifically not developing this as a full-blown epi study. To the extent that we can build into the refinement process activities that ordinarily have been characteristics of studies that are assessing causal relationships, we see that as a good thing. But this is really at its heart a signal refinement activity.

DR. BEHRMAN: Can I address a point as well? That, in a sense, doesn't matter so much to the agency what you're asking. In other words, we're trying to learn how to develop Sentinel, and any activity we do will teach us a lot about governance, communication, processes and procedures, (inaudible) development, and so forth. So, on one level, the question itself and where it fits in the paradigm, which I personally leave to the continuum, is less important this early in the game than the lessons that we've learned, and we learned a lot of lessons. Those of you who were at the Brookings roundtable where we talked about this -- where we said, ooh, look; we forgot to post this before it was mentioned publicly. That's an important lesson for us to learn, because, in retrospect, we want it posted and make sure that that the division in the company was aware. We were still trying to scramble and figure out who the sponsor was. So, we -- the little lessons and big lessons we learned. So, where it fits in the spectrum this early in the game is not that troubling to us.

DR. RACOOSIN: I think we are grappling with that question, though, and so by doing this and going through the process -- because we have had an expert panel on signal refinement, and one of the questions is well, where does that end and how can we produce actionable information in an efficient way. And so -- but we need a

place to start, and so we have a very, you know, productive process in developing this first protocol, and I think it -- you know, as Rachel said, you know, the lessons learned is a big part of this. So, now that we have -- is how can we think about adapting it for other products that we're interested in assessing MI for and adapting the methodologies that have been developed for it and evaluating the propensity score matching, the disease risk score stratification, and thinking about how these can be combined in future evaluations now that we've done the heavy lifting of creating it for this protocol. So, I think it's a key question as to how we can adapt these in the future, but we have a very, you know, well-developed protocol to start from as we move in the directions that we need to.

MR. MINES: Thanks.

DR. McCLELLAN: Thank you.

MR. HARE: Hi, there. I'm Jonathan Hare from Brazilian Network Systems.

First of all, I'd like to applaud the work you've done with Mini-Sentinel. It's seems a really appropriate and pragmatic way to get started. I do -- I would observe that there seems to be in the design of it some tension. It reflects some tension between the patient safety objectives and the need to preserve privacy and also respect the concerns of the various data partners. For example, the fact that data is analyzed at source and only the identified records are sort of aggregated. You lose the ability to get sort of the full longitudinal record from disparate sources for the same patient -- things like, for example, you actually want to know if they have behavioral health issues. If they're on -- you know, abusing drugs or alcohol in combination with certain drugs and other risk factors, you actually want to know that. You lose the ability to confirm

suspected results. You get, you a hundred million patient lives out there, you're going to detect all sorts of apparent risk factors, many of them real, many of them false. So, you lose ability to confirm from the patient or from the treating physician what are real events, and also you lose ability to give sort of personalized assistant support to the patient and to the clinicians, like, you know what should this patient be worried about.

So, I have really two questions. One is: Is my sort of assumption accurate that the design was, you know, sort of a concession to the constraints of available technologies to preserve, you know, basically deal with those different competing issues? And, second, when you go beyond Mini-Sentinel, do you see -- do you anticipate efforts to resolve the underlying tension? You know, how do you connect dots without filing 5(c)? How do you respect the rights of the data holders which we rely upon? And how do you sort of close the loop with the patient and caregivers so we really get the result we're all looking for, which is improve patient safety on a national scale?

DR. PLATT: I'd say our take all along has been that the principal needs have been to develop acceptable governance structures for what we're doing. The technical issues are not small, but they are small compared to getting to sort of a shared space where all parties can be fairly comfortable. In this coming year, we're going to be starting to test methods for doing linkage across data sources so that we can start to construct longitudinal records when we need to do that. And for that, as well, our take is that the technology will be important but the part that's going to take the most time and need the most care will be establishing rules that everyone is comfortable with and that we can post on our website and have all of us whose data will be linked across sources be satisfied with as well.

DR. McCLELLAN: Can you, I'm wondering, maybe clarify that --

Jonathan also brought up this confirmation question, so do you see something in the data? What about -- what capacity's in place to go back and verify the clinical accuracy of those administrative data or other findings?

DR. PLATT: All the data partners have access to full-source data when it's necessary. Kristin just described some of the issues about the -- sort of the legal underpinnings of that. One of the great strengths of this overall framework is the ability to use coded electronic data to do the really heavy lifting, be able to understand almost everything you need to know about millions of people and then to review the actual records a few hundred people when that's necessary. That's largely a manual process these days -- by and large the target is hospitalization records, and those -- almost none of those are available in electronic form, so that's -- that becomes a slow process. But it's one that everyone of our data partners has a substantial amount of experience.

DR. McCLELLAN: So, for example, in the saxagliptin site that you were talking about for patients that are suspected of having -- or that appear in the electronic data have MIs, there will be some kind of confirmatory process.

DR. PLATT: Actually, the plan is no, is that right, Bruce?

MR. FIREMAN: Well, there -- one of the advantages of starting with MIs is, unlike some other outcomes that we could have started with, there's already been a lot of work and a lot of study in our data partners, some of which I've been involved with at Kaiser Permanente validating the positive predictive value of the hospital discharge diagnosis of a MI, and so our choice of codes and criteria for including heart attacks, you know, has been based on that work.

But I will also say that in responding to the question that building infrastructure is gaining -- you know, we'll be gaining a lot of experience with this back

and forth process with the distributed data so that we'll be able to use the richness of the data that's available at each of the data partners, and it's going to get richer as we get -- more and more people have EMRs -- electronic medical records -- and keep the information local, keep privacy respected, but extract all the information that's useful for inference about the safety of the medical products. And so that we'll be going back and forth and there will be -- our analyses are stratified typically by site and health plan so that if there are coding and diagnostic and practice differences across these sites and we see an unusual number of them coming from one place, we can go back to that site and say hey, what's going on here during this six-month period when we see an unusual number of events and can go back and forth with people who are familiar with the courts and limitations of their own database and their own setting and do some of the validation that you're envisioning.

DR. PLATT: Having said that, FDA's taken a belt-and-suspenders approach. Although the data are fairly compelling that the codes for acute myocardial infarction actually represent acute myocardial infarctions, they also asked us to pull a hundred records and have them adjudicated by an expert panel, and we're about 80 records into that hundred-record validation. So, we'll have separate information telling us what the conformance characteristics of these codes are in the Mini-Sentinel distributed database.

DR. RACOOSIN: And I think a second goal of that project is to establish that process within each of the data partners so that when we in the future want to validate a particular outcome we already have procedures in place that have been tested so that we can efficiently get to those charts and validate them.

MS. ROSATI: I think one of the other important point to pick up on there

that he had mentioned is that by using a distributed data network, we were using summary aggregated data. It's difficult to communicate with the patients about the outcomes. Well, I think one of the intents here is to make sure that that communication process with physicians and patients is a controlled one so that preliminary data is not communicated, because it can cause false alarms that alarm the public and potentially cause them to get off drugs that would be very important and beneficial to their health. And so the fact that the communication and decision about the drugs is removed from the data partners I think is probably over the long term a very good policy decision.

DR. McCLELLAN: Thank you.

MS. JONES; Judith Jones, The Degge Group and long time ago FDA Safety.

I first wanted just to congratulate the effort. It's very exciting to see this come in to fruition, and I'm a perpetual optimist, so I think this will work and be demonstrated.

And so the question I have is looking to the future. FDA at any point in time may have 50, 100, or more signals that they could evaluate realistically in this data. Is there going to be, on the short term, any priority for perhaps the 20 that have been validated and then, a longer term, any notion about how this will be utilized and what the priorities will be? Will it be public health populations, severity, or what? It's a hypothetical question, but it would be interesting --

DR. BEHRMAN: I guess that's mine. Each center is -- this is a resource that's going to be available to each medical product center, and each center will -- setting in place, processes to tee up the priority list. We already have that problem. Again Sentinel is another -- already a new tool to help address the issues. We have -- always

have, I guess always will, if you will, more work than we can handle and resources that are always an issue. So, the notion of how to prioritize is based on many of the factors you mentioned. We've written guidance, for example, in the warnings/precautions guidance when we talk about how to prioritize what's put in labeling. We go through basically those elements, and we talk a lot about the impact on the population, and that has to do with severity, size of population, and I believe impact. So, all those will fix into our thinking.

Judy, you want to answer that?

DR. RACOOSIN: No, I just want to emphasize that the -- you know, as Rachel said, the use of an act of surveillance evaluation is one more tool to help us better understand what the particular safety issue is. And each of the centers already has in place procedures for identifying and prioritizing safety issues, and so, you know, this is an additional tool that's being incorporated into those procedures. And so it's really on a center-by-center basis by which they are determining how they want to enhance their surveillance capabilities with this tool.

I want to go to the side microphone over here. I'm trying to keep all these in order, but -- I'm doing my best.

MS. PENDERGAST: I, too, would like to congratulate on the progress that you have made.

I have a question.

DR. McCLELLAN: I'm sorry; can you identify who you are?

MS. PENDERGAST: I'm sorry. Mary Pendergast. I'm a lawyer in private practice.

My question goes to the results of this study whenever they occur.

Unless all the drugs have the exact same risk of MI, there's going to be some stratification among the drugs. Do you know now what you're going to say depending on what those risks are? I mean, is the answer going to be drug A has a higher relative risk than drug B? Or is -- how are you going to describe what you find?

And the my second question is if this is technically signal refinement -- you're saying we see a signal of a higher risk of MI with X drug -- do you know now and can you tell industry now what their next step is to resolve the question of whether or not it's a true or a false signal?

DR. BEHRMAN: I think that's mine. We are a data-driven agency, so we will look at the data and make the necessary regulatory decisions and then take the necessary regulatory action. And as an ex-FDA are you -- I think you know that, so if the data are sufficiently compelling that we believe that we need to change labeling, we will do so and will do so for the products that need their labeling change. If the data are compelling and we believe there's a class effect, we will initiate class labeling changes. It all depends on the data. And as Judy has emphasized a number of times, a Sentinel finding is one piece of the puzzle and it will be evaluated in the context -- by the way, by the medical practice center and the appropriate review division, not by the core Sentinel team that's responsible for organizing the initiative. We're not responsible for the review of the data. These data will be handled just the way we handle any other data. It's another piece of the puzzle.

MR. KRALL: Ron Krall from Penn Center for Bioethics and also a member of the OMOP Executive Board.

I have a question about the saxagliptin study, which really stems from the results from OMOP that we saw yesterday. I think it was striking to many of us that

the estimates of relative risk that we saw yesterday could vary tremendously based on the design choices that are made for the settings for different analytical methods that are applied to these kinds of analyses. To what extent do you --

DR. McCLELLAN: Excuse me, Ron, can you, just for benefit of the audience that wasn't here yesterday, maybe expand on that a little bit on what you mean when you say the differences in methods and implications for differences in relative risk?

MR. KRALL: It would probably be good if one of the principal investigators actually did that, but I'll summarize it briefly. What OMOP has done is carry out a set of experiments using drug health outcome of interest pairs and systematically explore the effect of studying the associations between the drug and health outcome pairs in different data sources using a variety of analytical methods and in those analytical methods a series of choices about how those methods are actually implemented. And the kind of bottom line of those results -- and I invite all -- certainly Judy to comment on that -- is that there's a lot of different -- you got a lot of different results based on the choices you make. And the question -- so that's -- that was kind of my takeaway from yesterday.

And the question I wanted to ask you is to what extent do you plan to explore the effect of the choices that you'd make in both design and in implementation of methods of analysis in the study of acute MI and the four oral hypoglycemic drugs?

DR. RACOOSIN: So, just to clarify one thing about Ron's description of OMOP experiment. The drug outcome pairs that were selected are known associations based on the medical literature, and so by testing the methods and the range of parameter settings on each of the methods on these known associations, there's a capability of measuring whether the method actually hits the mark. So, I think given the

results of the OMOP work, we are going to need to think about how to apply those lessons learned to the act of surveillance evaluations moving forward. I think we are very close to having just learned a lot more about the results of the experiment, and so as we move forward we'll need to consider how recognizing -- how all of those choices are made in the analysis, how those potentially impact what the results will be, and to think about how we can do that in an efficient way but recognizing the importance of questioning those choices and the ultimate -- how the ultimate result comes out.

MS. ANDREWS: Hi. Elizabeth Andrews from Research Triangle Institute, also a member of the Scientific Advisory Committee for OMOP.

I, too, am just floored by the progress that's been made, and partly because of the observations that were just discussed, I'm really delighted to see that this first example is learning from the lessons of many years of structured epidemiologic study, so I'm glad things are looking more like studies than they might have otherwise.

My question is about the governance structure that you put into place in which the decision has been to consider this not to be research but active surveillance. And you have the advantage of not going through the IRB review and approval process at each site, which can be -- while it can be very effective and necessary for human subject's research can also stand in the way of getting early results to pressing public health questions. So, I applaud you for doing that and I'm wondering how that lesson can be implemented for studies that are not directed by a public health agency. So, as I understand it, the Sentinel Initiative has been granted a unique status as a public health activity. Can that be done for studies that are sponsored by other organizations?

DR. BEHRMAN: I guess -- is that mine?

MS. ROSATI: And I'll follow after you.

DR. BEHRMAN: Okay. I don't think we've been granted -- we haven't been granted special status. We are a public health authority doing our job, and it's not research and we just had discussions at the OHRP and they confirmed that. I think there's, as we all know, a national discussion going on about what is research and what is not research and that this -- the notion that one creates general, logical knowledge, therefore it's research, seems to me counterproductive. But you've asked a very important. As we start to think increasingly about a national resource and other activities and who is conducting those activities and what questions they're trying to answer, it becomes very complex. If the Saxa study had been conducted by the drug manufacturer, would the positive procedures have been different? If we found a way to incorporate the manufacturer into Sentinel such that because -- and it was a post-marketing commitment we were directing, does that change its status. And now I will turn to the attorney.

MS. ROSATI: Picking up from what you were saying, you know, the distinction between public health surveillance activities and research is a very thin one, and there's lots of activity going on across the country to figure out exactly what that distinction is. OHRP, my understanding is, working with the CDC quite carefully to develop guidance for us on what that distinction is, which should be helpful. But, clearly, the kind of private industry to, you know, non-federal agency directive activities need some guidance out there, and we're just really crying out for that, because as you point out involving local institutional review boards is not a very -- it's a pretty unwieldy way to do the same type of research across the country, and we either need to provide really specific guidance for IRBs so that they review the study the same way, because if you variate across sites you can end up with a study that has less validity at the end. While we need to create a national institutional review board perhaps to review these big data

studies because local IRBs are not very well -- are not usually trained adequately to judge big data research. They're usually clinically trained, do a very good job at thinking about patient rights and interventional studies but often don't know much about the issues related to the big data research. So, that's -- you've really hit your -- hit the nail on the head in terms of what we need to do next.

MS. ANDREWS: Right, thank you very much. I hope that does stay high on the agenda for the next year or so.

DR. DeCHERNEY: I'm Steve DeCherney. I'm a professor of endocrinology and diabetes at the University of North Carolina in Chapel Hill, and so I had a methodological question about your study.

While it's clear that a very low blood sugar reaction can precipitate an MI -- no question -- there's also a fair amount of literature that suggests that the coefficient of variation around ambient glucose levels also contributes to the complications of diabetes, including the acute events. And I just wondered methodically how you take into account a drug that may actually cause less fluctuation, which actually may make it a safer drug than one that causes an acute drop in blood sugar.

MR. FIREMAN: Okay. Well, we will notice if this -- if one or another of our study drugs is safer, and so if the risk is lower after adjustment for whatever we can adjust for, for the co-morbidity and other covariate information that I outlined there. Now, lab values and other detailed clinical information we may be able to incorporate eventually down the road in Sentinel. But right now clinical lab values would have to be part of some kind of follow-up study. But were you asking can we notice, with our design, benefit as well as harm? Was that your --

DR. DeCHERNEY: No. I'm assuming you have access to hemoglobin

A1C data, but what you may not have are ongoing glucose logs or downloads from meters or those sort of things. I just wondered how you were going to take into account -- I mean, a very simple case is a patient who has a hemoglobin A1C of 9 who suddenly has an MI. Is that a different case related to a drug? Is that a different case than somebody who had a hemoglobin A1C of 6-1/2 and has an MI if you didn't know what those fluctuations were prior to the event?

DR. PLATT: That's really beyond the scope of this protocol. This is -- this protocol doesn't attend to mechanisms to explain the observed results, and that would be a good example of the kind of follow-up full-scale epidemiologic study that would be needed in the event that there was some difference between saxagliptin and one of the comparators.

DR. McCLELLAN: Is that something that's contemplated being handled in Sentinel-type framework at some point? You all have emphasized the dynamic nature of the data that are available. If, you know, additional -- you know, you could see at some point in the future, and I expect some of the Sentinel data holders right now have lab results over time and maybe even if they've got full electron record systems, the logs of glucose readings for patients and it seems like the potential is there. I don't know --

DR. CURTIS: Certainly.

MS. ROSATI: Yeah.

DR. CURTIS: Yeah, and over the next year, we're actually working now to sort of expand the common data model to include selected clinical laboratory data and vital signs from some of the data partners. As you can imagine, if it takes several months to create a common data model that is robust and a robust distributed database of administrative and claims data, it's a mountain to go up the clinical data, into the clinical

data realm. I think we're doing this in a way that makes sense. We're beginning with sort of -- in a manageable fashion. But when you start talking about bogs, things that are measured repeatedly over time, and then think about how to put that into some sort of distributed data environment, eyes get glassy quickly. So, I think there's a lot of important work to do. We're starting on that, and we'll look to continue in that direction.

MR. FIREMAN: So, since Lesley's responsible for it, she's been appropriately cautious. So I'll have to say that we've made a commitment to FDA to have consolidated hemoglobins and certain other lab test results available for use by this time next year from part of the population. So, we should be able to do a deeper dive using those kinds of data.

DR. McCLELLAN: Well, in taking it to the different version of Rachel's point earlier that this is a piece of all the evidence that's being developed (inaudible) involved, it might be difficult both from a data availability standpoint and another standpoint to have lots of sites doing these kinds of particular detailed clinical studies. You know, one does wonder whether having a network like this makes it easier to do complimentary studies or extension studies. You know, maybe you're not going to do this kind of glucose log analysis on particular drugs at every site, but if you really want to investigate further against more insights as to why you're seeing certain bottom-line patterns in terms of safety risk for particular drugs in the overall network, it seems like it might be something that could be a extension piece for certain sites or part of a more complimentary research or, you know, underline the causal -- analysis of the underlying causal mechanisms.

DR. RACOOSIN: I think one that is -- the way things are structured right now is that these active surveillance evaluations are part of the Mini-Sentinel and/or other

active surveillance pilots, but as things are structured right now at FDA, each of the centers has contracts with various databases for conducting formal studies. And so right now the way things are structured, something like that would move into the center who has the question to develop and -- not to say that there isn't much overlap between the Mini-Sentinel data partners and each of the databases that the centers have contracts with, but just logistically it's not currently part of what we're envisioning as part of Sentinel.

MR. FIREMAN: While I share that vision and also note your caution, I just want to say that we do have clinical experts working with us at the different sites -- endocrinologists and diabetes experts -- and so we'll be thinking through ways in which bias might arise from some of these sources, and the main issue here is are the people who are becoming new users of one or another of our study drugs likely to be different in some unmeasured way related to some of the clinical measurements that we don't have access to. So, we'll be thinking about that and cautious about the limitations of our work, you know, as these considerations may arise, and hopefully in the future we'll have more data to address them directly.

DR. LIPKIN: Yes. I'm Paul Lipkin. I'm a pediatrician with a special interest in special populations, and I'm a health policy fellow with the Robert Wood Johnson Foundation.

When this clearly very rich database with tons of important information that could be gleaned from it -- however, when I look at the population distribution curve, my eyes focused to the left, which is young children, but at the same time to the most elderly, and the numbers of people represented in your samples at this point are really quite thin at either ends of the age curve. Question in my mind therefore is do you think

the Sentinel Initiative will be able to adequately look at these special populations, particularly because they are often the most vulnerable medically?

DR. CURTIS: I can take that and then add to it. I mean, ultimately, yes, the goal is to have a robust system that serves the entire population of this country. That said, we have to start small, start with what's easiest, if you will, and cheapest to get and then learn how to do it well and expand carefully. One reason we've made as much progress as we have is we've been very careful and judicious and have with a laser-sharp focus. So, the answer is absolutely yes. How quickly will depend on resources and the availability of the data. I was thinking back to one of the questions that was asked in terms of looking at information longitudinally, and if only the current state of data standardization was such that we were limited by our governance and our ability and our resources -- in fact, we all know that the state of data out there is not what it should be and the populations you're talking about are often either underserved or hard to get hold of. So, that is the intent. We will get there. How quickly we'll get there is a question that's extremely hard to answer.

DR. McCLELLAN: Well, now, one piece of --

DR. RACOOSIN: Can I just answer that?

DR. McCLELLAN: Go ahead.

DR. RACOOSIN: Is that we do have our federal partners collaboration, which includes Medicare, Medicaid, populations, as well as the VA and the Department of Defense, and so we have been able to -- you know, the data that Leslie presented is -- you know, the groups captured within the Mini-Sentinel population, but in addition to that in our federal partners collaboration, we are accessing, you know, many older people in this country as well as within the Medicaid population we can access younger people who

are in the lower economics population.

DR. McCLELLAN: So, that was -- my follow-up question was, I mean, look, you're not going to be able to get to a representative sample in filling out the vulnerable populations, either higher age ranges or the lower ranges, without including federal program beneficiaries of Medicare and Medicaid, and since there are so many activities ongoing now with the FDA's Federal Partners Program, it may be worth spending another minute on that. And then my question was how does that -- how does the analysis that's going on in that work match up with the analysis that's envisioned with the Mini-Sentinel and further Sentinel efforts that are relying on private sector partners?

DR. CURTIS: Right. So with our federal partners, there's really -- prior to the Federal Partners Collaboration, there was established the Safe RX Project, which is a project between FDA and CMS that was launched shortly after the Medicare Part D data became available for research purposes. And so through that Safe RX Project, within FDA across the medical product centers there are a number of projects going on involving Medicare and Medicaid populations that are both formal, pharmaco(epi) types of projects as well as active surveillance-oriented projects. So, that is ongoing.

And then around a year and a half ago we launched the Federal Partners Collaboration, which brought in, in addition to the Medicare and Medicaid populations, the VA and DoD. And so we have been able to look at some questions that have arisen that are of interest of the three organizations, and as we get -- and some of this work has been published or presented already, so some of the work that Sieber has done with flu vaccine surveillance for Guillain-Barré syndrome, et cetera, things -- those kinds of active surveillance efforts have been presented in pharmacoepidemiology forums. And we've additionally presented results of some of the methodology work that we've done to try

and understand how easy is it to use Medicare data for the purposes of active surveillance evaluations. And in some of the projects that are being worked on now will be presented or submitted for presentation at upcoming meetings. So, while I'm not going to get into specifics of projects right now, I think the goal is certainly to address questions that are arising in these populations that are of interest to a range of federal partners.

I think the question that you raise about how does that coordinate with Mini-Sentinel -- I think certainly there are some questions that would be useful, especially once we have developed the protocol in the Federal Partners Collaboration to also implement it within the Mini-Sentinel so that we can get broader input into whether these issues are real problems.

DR. RACOOSIN: Well, Mark, if I could just -- I mean, one can envision at some point in the future there's the Sentinel, which is the national program, and the agency -- the various pieces that are informing building that will somehow coalesce, but we can't predict precisely how that will happen. But full lab studies at that point will probably be done under that umbrella as would capturing the rest of these populations.

DR. McCLELLAN: And broader distributed network.

Ron, your first question was a good question, so you can ask another question. I just thought I'd get a sense of like who -- Paul, any other questions there? Okay, so we'll finish with these two and then break for lunch.

MR. KRALL: Thank you. I'll try not to ask a good one so that I get to ask a third.

I ask this actually as a member of the OMOP Advisory Board or, rather, Executive Board.

You guys had many Sentinel and, ultimately, a Sentinel or on the sharp end of the stick OMOP has been conceived of and implemented as a research project. My question is to what extent have you been able to take advantage of the tools, a common data model, the data characterization tools that OMOP developed, and if you had advice for OMOP today about what its focus should be over the next two years in its research program, what would that be?

DR. PLATT: So, we've been -- I'd characterize us as OMOP's most interested consumer. And so we've been watching with terrific interest what's going on. Since yesterday's sort of the first time the full sort of breadth of the findings have been available, we're ready to sort of dive in with OMOP to sort of talk about where are the lessons that we can adopt and to plot a shared strategy.

After this meeting ends but before we all go home tonight, we're sitting -- 10 or 12 of us are sitting down -- Mini-Sentinel, OMOP, FDA -- to talk in some detail about starting to build the shared agenda for this coming year. So, it's clear that OMOP has so much -- has so many results. I think our next job is to figure out which of those results is relevant to the work we're doing -- and to this protocol in particular, because -- so for those of you who weren't here, if you had to say one thing about the OMOP results, it's some methods seem to work in some environments sometimes, and I think what we have to do is ask in the environments we're working in for the questions we're asking which methods are most useful. So, I think the next order of business is for us to start doing that deep dive with OMOP to try and make sure that if there are flashing red lights we stay away from them, and if there are particularly appealing approaches that we implement them.

DR. McCLELLAN: Paul.

DR. STANG: Mine is just a quick question. It's --

DR. McCLELLAN: Identify yourself.

DR. STANG: Sorry, Paul Stang, Johnson & Johnson and OMOP.

It's more opportunistic, so, Bruce, if I understood your presentation correctly, you're essentially concurrently able to do observational analyses as a large clinical study will be ongoing. And I don't know the details of the large clinical study, but it appears to me that you also have the opportunity to take the inclusion/exclusion criteria being used in the large clinical study and apply them to the observational data and look to see the extent to which they are concurrent with each other and maybe inform ways that we can do better at interpreting why observational studies may or may not always be consistent with findings from large randomized studies. It just seems to me it's a unique opportunity, because they're happening at the same slice in time, which is not usually the case. Usually the clinical trials or something has happened in the distant past. So, I'm just curious if that's come up in any of the discussions.

MR. FIREMAN: Well, as we were talking about earlier, we at Kaiser Permanente anyway, because we have electronic medical records we can -- if signals arise or findings arise or disparate results like what was referred to before from OMOP when we use one method we find one thing, when we use another method we find something else. We do have the capability to look at much richer clinical data that might be helpful, and I know you have experience looking at some of our data on, what, EKGs I think.

DR. STANG: Right.

MR. FIREMAN: And so we have, you know, a lot of data online that we could amplify this. But what we're planning here, in the plans that I presented here, we're

relying on data from Kaiser that's comparable to the claims-based and administrative data that's in the other databases and these supplementary efforts -- which I think are very intriguing that you've mentioned and that arose a few minutes ago in discussion -- I think there are intriguing possibilities, but they aren't yet planned out in (inaudible) our protocol.

DR. STANG: Okay, because I was thinking --

MR. FIREMAN: What's the promise of --

DR. STANG: Well, I just think it's an opportunity to take what -- I'm oversimplifying, I'm sure, the clinical study, but their inclusion/exclusion criteria in the clinical study, many of which I think could be applied to the observation -- there were 23,000 or so people that I think you're going to identify to look at the relationship in this case between observational data and clinical studies. It's -- to me, it just seems like a pretty unique opportunity that you might want to discuss. I think it could be pretty cool to do.

Thanks.

MS. ROSATI: Just in time for the year 3 work plan. Thank you, Paul.

DR. STANG: Well, I figured why not.

DR. McCLELLAN: Good idea, thanks. Any final comments from the panelists on any of the issues that have been raised?

All right. I'd like to thank you all very much for driving a very interesting discussion. We are now breaking for lunch, and a reminder that lunch is on your own. In the packets, there's a list of local restaurants that are close by. In addition, our host here at the hotel wanted me to let you know that there is a lunch special upstairs -- soup and sandwich $10, and that'll be quick. We are going to start again promptly at 1:15, and in

addition reprints of that *New England Journal of Medicine* article are at the tables. If you don't have a list of restaurants in your packet, those are at the tables as well. Thank you.

(Recess)