

THE BROOKINGS INSTITUTION

SECOND ANNUAL SENTINEL INITIATIVE WORKSHOP

Washington, D.C.

Monday, January 11, 2010

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

**TABLE OF CONTENTS:****Welcome, Introduction, and Meeting Objectives**

Mark McClellan, Director, Engelberg Center for Health  
Care Reform at Brookings p. 5

**Keynote Address**

Margaret Hamburg, Commissioner of Food and Drugs p. 13

**Session I: Reports from Selected Sentinel Contractors****An Analysis of Legal Issues Related to Structuring FDA  
Sentinel Initiative Activities**

Kristen B. Rosati, Partner, Coppersmith Schermer &  
Brockelman PLC p. 38

**Defining and Evaluating Possible Database Models to  
Implement the Sentinel Initiative**

Jeffrey S. Brown, Lecturer, Department of Population  
Medicine, Harvard Medical School and Harvard Pilgrim  
Health Care Institute p. 59

**Evaluating Existing Methods of Safety Signal  
Identification for the Sentinel Initiative**

Jennifer Nelson, Associate Investigator, Biostatistics  
Unit, Group Health Research Institute, and Affiliate  
Assistant Professor, Biostatistics, School of Public  
Health, University of Washington p. 80

**Session II: Update on FDA's Current Medical Product  
Safety Initiatives****Update on FDA's Current Drug Safety Initiatives**

Janet Woodcock, Director, Center for Drug Evaluation  
and Research, Food and Drug Administration p. 101

**Observational Medical Outcomes Partnership (OMOP)  
Overview and Lessons Learned**

Patrick Ryan, Manager, Drug Development Sciences,  
GlaxoSmithKline Research and Development, and OMOP Co-  
Investigator p. 114

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

**Update and Work Plan for Mini-Sentinel Contract**

Richard Platt, Professor and Chair, Department of  
Population Medicine, Harvard Medical School and  
Harvard Pilgrim Health Care Institute p. 127

**Session III: Issues of Broad Interest in Implementing  
Active Surveillance****Ensuring Patient Privacy while Meeting Public Health  
Needs**

- Donald O. Beers, Associate Chief Counsel for  
Drugs, Food and Drug Division, Office of General  
Counsel, U.S. Department of Health & Human  
Services p. 162
- Verne Rinker, Health Information Privacy  
Specialist, U.S. Department of Health & Human  
Services p. 167
- Jeffrey C. Torres, Partner, Lathrop & Gage LLP,  
and Vice President and General Counsel, Qual-Rx,  
Inc. p. 170
- Deven McGraw, Director, Health Privacy Project,  
Center for Democracy and Technology p. 176
- Kristen Rosati, Partner, Coppersmith Schermer &  
Brockelman PLC p. 184

**Sentinel as a National Resource for Safety Science**

- Ronald Lee Krall, Associate Fellow, University of  
Pennsylvania Center for Bioethics; Former Senior  
Vice President and Chief Medical Officer,  
GlaxoSmithKline p. 213
- Arthur L. Holden, Chairman and Founder,  
Pharmaceutical Biomedical Research Consortium,  
Ltd.; Chairman, CEO, and Founder, Serious Adverse  
Event Consortium, Ltd. p. 221
- Francesca Cunningham, Director, Center for  
Medication Safety PSCI, Program Manager  
Pharmacoepidemiologic/Outcomes Assessment,  
Department of Veterans Affairs p. 231

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

- Judy Racoosin, Sentinel Initiative Scientific Lead, Office of Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration p. 245

**Building a Multi-Purpose Network for Enhanced Use of Health Information**

- Carolyn Clancy, Director, Agency for Health Care Research and Quality p. 269
- Paul Stang, Senior Director of Epidemiology, Johnson & Johnson; Principal Investigator, Observational Medical Outcomes Partnership p. 282
- Rachel E. Behrman, Acting Associate Director for Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration p. 290

**Closing Remarks**

Mark McClellan, Director, Engelberg Center for Health Care Reform at Brookings p. 324

\* \* \* \* \*

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

## P R O C E E D I N G S

DR. McCLELLAN: We will have a very busy and full day given all of the progress taking place on Sentinel Initiative and Post-Market Surveillance.

My name is Mark McClellan. I'm the director of the Engelberg Center for Health Care Reform at the Brookings Institution. We are delighted to be hosting today's second annual Sentinel Initiative public meeting. As you know, improving our ability to conduct active surveillance of medical products is a fundamentally important topic both for better science and progress in health care reform, as well as a fundamentally important topic from the standpoint of public health and the American people. It's a critical component of all of these efforts to make our health care system work better.

Some of you may remember back in December 2008, just a little over a year ago, there was a public workshop much like this one that laid a framework out for some of the major issues and challenges to be

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

addressed in conducting post-market surveillance. Now, that workshop was much more about framing a general approach to post-market surveillance. This time, a year later, we're pleased to be hosting a second workshop to talk about some of the progress that's been made. So you're going to see more presentations today of actual initial implementation efforts, as well as some of the many issues that continue to need to be addressed as we move forward.

So we're going to go around further on some of the important challenges like maintaining safety and using systems that are developed for post-market surveillance to help us improve evidence and knowledge in other areas as well. This is an effort that reflects the commitment of the Food and Drug Administration. They have from the start wanted to ensure that the Sentinel system is developed through a public and transparent process. And so the support for this meeting is part of a larger effort by the FDA to encourage that kind of dialogue and awareness.

As part of that effort, since early 2008, the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Engelberg Center for Health Care Reform at Brookings has been convening a series of meetings and technical workshops on specific topics for addressing some of the challenges and the solutions to those challenges to achieve better post-market evidence.

So following on all of those efforts so far, today's workshop is designed with a couple of objectives in mind. First, the intent is to provide an update to all of you and everyone who takes advantage of this meeting over the Internet on the current status and the future vision for the Sentinel Initiative. And then second, we hope to engage the stakeholder community in a discussion around these kinds of implementation activities and the key challenges, and issues, and potential directions for solution. This is meant to be an interactive discussion as part of an interactive process. And so we're looking forward to the participation of all of you at specific points throughout the day.

To get us started right away I'd like to tell you that I'm very pleased that Commissioner Peggy

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Hamburg is joining us this morning. She's going to set the tone for this workshop and help lay out some key issues in her opening remarks. Then, during Session 1 this morning we're going to hear reports from a group of contractors who are working with the FDA already and have recently delivered reports on issues including legal and privacy topics, possible data models that could be used for post-market surveillance, and statistical methods for safety signal identification. Sounds technical, but as you know from last year's meeting from following these issues up to now, it's solving the set of practical issues together that's going to enable the Sentinel Initiative to have the largest possible impact.

In Session 2 we're going to have an opportunity to learn about some of the current pilot projects that are already underway with the Sentinel Initiative. These are projects that are developing and testing the kinds of infrastructure and data tools and methods that are going to be needed for Sentinel to carry out its intended purposes.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Then, after a lunch break, the afternoon sessions are going to include three panel discussions on a range of issues and challenges that continue to be important and need to continue to receive active attention for the effective implementation of the Sentinel Initiative. This includes assuring privacy while meeting public health needs. It includes how Sentinel can potentially serve as a national resource for safety science going beyond the Sentinel Initiative itself. And also includes going still further -- the potential for Sentinel to contribute to a multi-purpose network or infrastructure -- national infrastructure for using health information more effectively to gain better evidence.

Now, before we get started I'd like to also mention a few housekeeping items. First, I want to remind you that this workshop is being audio recorded. We're going to make this recording available afterwards. And so everything said is on the record today.

There are standing microphones, as you can see, around the room in the center of each aisle. Those

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

are for questions from all of you. We're going to have some time and I'm going to try and stick to the speaker time limits to make sure that we have time to include questions from all of you. When you come up to the microphone, please be sure to give us your name and your affiliation and then get right on with the question or comment.

For the speakers and panelists who are here today, first of all, thank you. I'm going to thank you again later. But I'd also like to remind you that we're on a tight schedule and we want to make sure that the prepared remarks stick into the allotted time limit so that we can keep the discussion moving and make sure we have an opportunity to hear from all the perspectives. And our timekeeper, Nadia, right here in the front row, right there, is available to assist you and remind you. And so am I.

And then finally, there are going to be three breaks during the day, including lunch for an hour on your own. There are a number of lists and maps the hotel has provided of restaurants in the immediate area

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and then we're going to reconvene in the afternoon after that.

So, let's get started. To begin the workshop, I can't think of any better way to do it than with the speaker who we have this morning for our keynote address, Dr. Peggy Hamburg, the Commissioner of Food and Drugs.

Dr. Hamburg was confirmed last May by a unanimous Senate voice vote, something that's not that common in this day and age. And as most of you know, there's a good reason for that. Dr. Hamburg is an accomplished and widely respected medical doctor and scientist and public health executive with the unique combination of both scientific expertise and management experience, practical leadership experience in getting things done to improve public health.

Prior to coming to the FDA, she held a range of leadership positions, including the assistant director of the National Institute of Allergy and Infectious Diseases; the commissioner of the New York City Department of Health and Mental Hygiene. She also

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

had academic appointments at Columbia University School of Public Health and Cornell University Medical College. She's also served as the assistant secretary for policy and evaluation in the U.S. Department of Health and Human Services in the Clinton Administration -- the first chance I had to work directly with her -- and is vice president for Biologic Programs at the Nuclear Threat Initiative.

Since her confirmation, Dr. Hamburg has outlined an ambitious and clear agenda for the FDA that includes not only protecting and promoting the public health in general, but a set of specific, major goals, strategic goals for the Agency that include improving biomedical science and improving medical products safety surveillance. So the activities of today's meeting are right in the wheelhouse of Dr. Hamburg's priorities for the Agency itself.

After her remarks this morning she's agreed to take a few questions from all of us. And so, Peggy, we're honored. We're delighted to have you here with us today to kick off this meeting. Thank you very much.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

(Applause)

DR. HAMBURG: Well, thank you very much, Mark, for that generous introduction. And I'm very pleased to be here. I was told that this was a workshop, but this is a mighty big workshop by my standards. But it's great to see the level of engagement around this important topic.

And I'd really like to begin on a personal note by saying how much I really appreciate Mark McClellan for his friendship and his support. Although most FDA commissioners deal with the challenge of always needing more -- more resources, more staff, more funding, more legal authorities to name just a few -- we tend to actually have a surplus of advice and opinions from all kinds of people. And some of it is helpful, and some of it isn't. But I can tell you that Mark's guidance has been particularly valuable to me because he is smart and has good judgment, but he also has the unique experience of having sat where I now sat. And he knows firsthand the realities and challenges of leading what I believe to be the most important public health

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

agency in the nation.

And I think that we are all fortunate that he has chosen to continue to devote his career to the goal of enhancing public health in the first place and FDA's ability to achieve its critical public health mission. So, thank you so much Mark for your work on this important initiative, but also on so much else of what you do.

And, of course, the reason that we're gathered here today to engage in a deep and meaningful way in work that will produce the methodologies, technologies, safeguards, and guidelines, which as a whole will illuminate the way forward to a new era of medical product safety is critical to the mission of the FDA and to the goals that both Mark and I have shared as FDA commissioners.

I use the term "new" in a qualified but deliberate way. Of course, the FDA's focus on medical product safety is not new. The Agency was founded more than a century ago for the expressed purpose of assuring the safety of America's food and drugs. Yet, the FDA's

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

legal authority to accomplish that mission has expanded and evolved significantly over the past several decades. And the enactment of the FDA Amendments Act, or what's fondly called FDAAA, in 2007, gave the Agency significant new authorities to protect the public from undue harm relating to drugs and medical products.

Along with new authorities, FDAAA requires the Agency to broaden its view of medical product safety to the horizon of the post-market environment. While the promise of such an approach has been recognized for quite a while, I can tell you that few things focus the attention of a regulatory agency, such as the FDA, more than congressional mandates that specify ambitious goals with date-certain deadlines.

And, of course, Sentinel represents an important element of this new approach. An initiative to create a national electronic safety surveillance system that will enhance FDA's ability to conduct monitoring of the safety and emerging risks of FDA-approved medical products. Section 905 of the statute sets the goal that the FDA will have access to data from

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

25 million patients for the purpose of post-market safety surveillance by July 1, 2010, which is less than seven months from today. So there's a lot of critical work to be done.

And while I firmly believe that public health protection is a critically important role of government, I also know that there are some things that government agencies cannot and should not do alone. The FDA has a vast and far-reaching mission, and our work represents a core responsibility of government in so many ways. But I also strongly believe that it's important for government leaders, like myself, to have the wisdom to recognize where and when it makes sense for us to develop partnerships with important experts outside the government.

And when it comes to convening a broad and diverse group of stakeholders to help establish the framework for a new safety surveillance system that will have a huge impact on society far into the future, it's essential for the Agency to find partners who have the right kinds of expertise. And I must say that the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Engelberg Center is uniquely qualified in facilitating the kinds of meaningful exchanges that must take place in order to make progress in an endeavor as ambitious and as important as Sentinel.

In the lexicon of the policy world in which so many of us operate, it's easy for certain words to degenerate into meaningless buzzwords through overuse. But in the Sentinel Initiative, we have an endeavor that enables us to reclaim the deepest meaning of some of those well-worn terms. By its very nature, Sentinel must be transparent because when we're dealing with information contained in millions of patient records, we must be completely open, honest, and public about what we are doing and why. And in what is done to safeguard the privacy of patients and assure that their medical records are secure.

By its very nature, Sentinel exemplifies the public-private partnership on quite a large scale. It is a collaboration made possible through the active engagement of public and private sector health care providers, companies, insurers, scientists, and of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

course, thought-leading stakeholders like all of you who represent a broad spectrum of interests and perspectives throughout society.

Through this collaboration, the framework that will advance the science of drug safety and enhance the protection of the public health will be created. By its very nature, Sentinel illustrates the incredible power of leveraging science and technology in order to achieve important public health goals. This is more than a significant change. I really do think it's a fundamental transformation. In a historical sense, it's an inevitable evolution of science, technology, and policy that will enable the FDA to use the full range of tools it now has under statute to protect patients from undue harm.

While the capability of my millions of patient records for evidence of an emerging risk will empower the FDA to accomplish its mission in new and powerful ways, it is a goal that many of you realized early on is essential to a fuller and more accurate understanding of the relative risks and benefits of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

medical products. We've long known that even the best pre-market clinical trials can track the impact of a drug only on a relatively small and carefully selected sample of patients for a limited period of time. The data that we glean from these trials stops far short of giving us a full picture of what really happens when hundreds of thousands of patients actually use the drug. And in the case of therapies for chronic conditions, they may be using these drugs for the rest of their lives.

Clinical trial data cannot anticipate or account for the variability of each individual patient, encompassing multiple factors such as genetics, personal health habits, environmental influences, pre-existing conditions, and drug-drug interactions. Today, more than ever before, those variables are critical factors in determining whether a particular drug is suitable for a particular patient. To an increasing degree, we're immobilizing the potential of pharmacogenomics or personalized medicine to enable the Agency to achieve a finer attenuation of the risk-benefit balance by helping

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

us understand which patient subpopulations may face an increased risk from a particular medical product and which patients are most likely to realize the therapeutic benefit.

We also recognize the expanding role of medical products in health care today often are the most vulnerable patients. It's striking that next year the leading edge of the huge demographic bulge known as the Baby Boomers will turn 65. By 2030, nearly 71 million Americans, or about 20 percent of the population, will be older than 65 and more than half of them will take medication every day to manage age-related chronic conditions, such as Type 2 diabetes, high blood pressure, and arthritis.

So in this, the beginning of a new era for drug safety, protecting public health means that the FDA's responsibility doesn't end when we grant a product pre-market approval. That is merely the first checkpoint in assuring safety. A fuller and more accurate picture emerges when a drug enters the real world of the mass market. And the FDA's responsibility

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to actively monitor and act on safety risks which emerge in the general population is one that extends for the entire time that those products remain on the market. This lifecycle approach, as codified in the statute, is a critical advance in public health protection.

And at the heart of FDA's ability to meet these responsibilities are the members of the Agency's Safety Review staff, many of whom are here today. These safety review teams are comprised of a wide range of experts in disciplines like pharmaceutical science, clinical medicine, toxicology, chemistry, and epidemiology in public health. Together, they practice the safety focus science of pharmacovigilance.

Sentinel will give them a powerful tool in conducting near real time surveillance in the post-market environment. Ultimately, with a fully functioning Sentinel System that has the ability to query millions of patient records at a time, they will be able to detect patterns of emerging risk far more effectively and at an earlier point in the lifecycle of the product. After detecting a risk signal, they'll be

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

able to further evaluate whether the early pattern can be strengthened and validated to provide an accurate picture of the measures required to mitigate the risk.

If a heightened risk is identified and confirmed, the Agency may then require a range of measures to alert health care providers and consumers about the new safety information. These measures may include product labeling changes and requiring the manufacturers to develop a risk evaluation and mitigation strategy, or REMS, for that particular drug. In many cases, the FDA will require that a medication guide fully explaining the new safety information is provided to every patient who has a prescription filled. Depending on the nature and severity of the risk, the Agency may also do targeted outreach to health care professionals and pharmacists.

In cases where significant risk to certain patients is clearly identified, the FDA will take appropriate action to protect the public. This may include placing restrictions on who may prescribe the drug and also under what circumstances an at-risk

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

patient may take the drug. For example, if we know that a drug is likely to cause birth defects, we may require that a woman of childbearing age produce the results of a negative pregnancy test before she can get a monthly prescription refill. This is just one illustration that the FDA will do what's necessary to prevent harm to at-risk patients. And in doing so, the Agency ensures that the drug continues to be available to all other patients who derive benefit from the drug.

The statute also gives the FDA the authority to require a company to conduct safety studies and clinical trials if a potential safety risk emerges in the post-safety -- in the post-market environment.

As of today, the Agency has asked companies for about 180 post-market safety studies of clinical trials. The results of these studies will give the Agency a clearer picture of elevated risk and help us to determine the appropriate course of action for risk mitigation.

Underpinning the FDA's heightened attention to post-market safety vigilance and action is the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

recognition of a fundamental truth. The scales of the risk-benefit balance are never frozen in a particular point in time. They are constantly shifting. With robust post-market safety surveillance and the tools we now have under the law, the FDA can endeavor to continually adjust those scales so that therapeutic benefit will always outweigh the potential risk to patients.

These new methods of protecting patients and consumers will become possible because all of you in this room have chosen to help. You have developed years to the study and mastery of particular disciplines and areas of expertise which meet at the nexus of Sentinel. The work you do and have done for years in the fields of consumer advocacy, privacy rights protection, health care, medical product development in science is not new to you as individuals. What is new is the fact that we've come together and that we've arrived at this particular point in time where the technology has matured, expectations have been raised, authorities have been codified, and hopefully, all roads lead to the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

intersection of enhanced safety monitoring and better options and outcomes for all patients.

There is a powerful alchemy that results from the result of convening all of you in one place at the same time and of focusing your expertise, experiences, and points of view on the issues at hand. In this effort, you're grappling with fascinating and important questions, such as how can we protect patient privacy and ensure the security of data while enabling access to data with enough detail to produce research that's scientifically robust and clinically useful.

How do we design a common data model so that data sets can be compared and analyzed in a meaningful way? And how do we reach consensus on the types of methodologies and protocols that should be employed in the quest to prove and disprove causal relationships between a product and an outcome? The process will involve a great deal of time and effort, open minds, a posture of objective inquiry, and along the way there'll be encouraging results, dead-ends, exhilaration, and frustration. When it comes to discovering new ways of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

accomplishing important things, we all know that we sometimes learn from the false starts and dead-ends just as much as we learn from easy early successes.

But I'm confident that a decade from now the important questions you're grappling with today will be well addressed, appropriate methodologies firmly established, and the processes embedded in the way FDA establishes safeguards for patients. I am confident that a decade from now the American people will be safer because of the work you're engaged in today.

And as FDA Commissioner, I believe that perhaps the most important thing I can do is to support and encourage you in that work and probably, to conclude my remarks so that you can actually plunge into it.

So, with deep gratitude, I thank you for your service to the FDA, your service to public health, and truly your service to the nation. Thank you very much. And I'm happy to take some questions. (Applause)

DR. McCLELLAN: Peggy, thanks very much for those remarks. We do have time for a few questions. Again, microphones are located in the middle of the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

aisles.

And while people are walking up, Peggy, maybe you can comment briefly about -- we've been hearing a lot lately about the new spending on information technology, new regulations coming out, and so forth. And while a lot of the attention has focused on CMS and the Office of the National Coordinator, it seems like a great investment in resources and infrastructure to support the kinds of data that could in turn be a big part of Sentinel and other FDA public health initiatives.

Is the FDA actively involved in those efforts? Could you say a little bit about how you see that fitting into your public health goals?

DR. HAMBURG: Well, there has been a huge push in information technology in many ways. And, as you know, you probably played a hand in helping to shape some of the new resources that FDA has achieved to build infrastructure within our Agency to support major and important information technology initiatives, including those such as this one. And I would be dishonest to say

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

it's been a completely smooth road building some of that infrastructure and expertise, but it's been very important. And now is a critical time for us to really make sure that what we're doing integrates with broader activities, both within the department and beyond. And I think Sentinel in many ways is an important pathway for helping to assure that kind of connectivity and interchangeability of systems and approaches.

But with the major new focus through health care reform and other activities on developing electronic health records and really drawing on computer-based strategies for delivery of care and assessment of quality of care and effectiveness of care, there are huge opportunities. We've been involved to some degree, but we've not been at the center of those discussions. But we have an important investment. Obviously, for an activity like Sentinel, the ability to connect with a whole new world of electronic patient records and medical information is hugely important. And it's important in many other domains of our activity.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

I also have to say I was surprised to learn that the FDA has an important responsibility actually in the oversight of electronic health records as a medical device. So that's an interesting set of questions that we are beginning to really examine and explore how we provide that important oversight role. But it is critically important. And reminds us of the way that FDA affects so much of what's going on in the medical care system and in public health in ways that are expected and unexpected.

DR. McCLELLAN: It's true, they are making health claims. Over here.

MR. SAN GIORGIO: Joe San Giorgio , George Washington University. Dr. Hamburg, thank you for your work and your comments.

I was hoping you could elaborate a little bit more about the safeguards for patient privacy currently in place with Sentinel. And related to that, how does Sentinel fit in your view into the current debate over health care reform?

DR. HAMBURG: Well, I think, you know, that

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the issues around the safeguards on patient privacy and the protection of important personal information has to be at the core of all that we do. And I would actually say that part of the task that we're looking to all of you for is to help us think through the complexities of those issues. There obviously is a legal framework that we work within -- the HIPAA regulations being a very important element of that.

But I think that we need to step beyond simply, you know, what's in the regulations, but also think about the broader context. And we need to make sure that people understand what protections are in place. And we need to have that framework. We also, of course, need to communicate the huge benefits that accrue from this kind of a system. So it's a bit of a delicate balance. But I'm hoping that this group -- and I know that there are experts in these issues -- will provide a very important voice around the issues of patient protection and safeguarding the privacy.

DR. McCLELLAN: It'll definitely be a topic for later today.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Keeping an eye on the clock I think we have time for two more questions if you all can keep them brief.

MR. PETRANAS: Joey Petranas from Genentech Roche. Thanks for your comments, Dr. Hamburg.

Two questions. One, you mentioned that the FDA seems to be or is the most important agency for public health safety. It seems to be that there are other agencies that think that as well. And I'm wondering if there's some kind of competition here between the agencies that might be coordinated somehow. So I wanted to hear comments on that.

And second, patient reported outcomes, both at the FDA and elsewhere, are becoming of increased focus. What's your vision on social networking through the Internet to facilitate that?

DR. HAMBURG: On the first, you know, I suppose it's probably not all that helpful to have a competition for who's most important. But I say it to underscore that FDA truly is a critical public health agencies, unlike any other agency, you know, in the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

nation. FDA regulates products that account for about 25 percent of the U.S. economy and the products that consumers buy. And we touch the lives of Americans every day throughout the day, you know, from the toothpaste you use in the morning and the breakfast cereal you eat, to the medications you might take; sun lotions or skin creams you might use; the microwave oven you might heat something in; the electronic health record you might -- your doctor might use. You know, so many ways. And we tend to be forgotten in that role and thought of more as a black box regulatory agency that just, you know, we have our checklist and we review things.

But our mission is so much broader. And we really sit at a critical point between opportunities provided by investments in biomedical research, discovery, and innovation, and the delivery of new medical products to people who need them. And I think that should not be forgotten.

But we are working very closely with other public health agencies and other nongovernmental

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

organizations that are critical to supporting health preventing disease and enabling, you know, a higher quality of life. So I think that, you know, we do sit in a very unique position. We are truly a public health agency and we best achieve our goals through partnership inside government and outside.

Your second question I've already begun to forget.

MR. PETRANAS: Social networking and outcomes of patient (inaudible).

DR. HAMBURG: Social networking is very, very important. You know, I think it's hard for me because I have to confess that I'm a little bit of a Luddite and I'm still having trouble using my BlackBerry. But, you know, we really have to, I think, respond to how people communicate in the modern era. And social networking, you know, is a hugely important aspect of how information gets communicated, exchanged, digested, and a mechanism by which important new ideas and connections can get made.

DR. McCLELLAN: Thank you. And last

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

question?

DR. CHRISTOPH Okay. Gary Christoph,  
Northrop Grumman.

We met several years ago, I think, when I was the first CIO at CMS. So, I'm -- thank you for your remarks. I think that IT is an important part of what we're doing.

The question I put to you is should we interpret your presence and the presence of other luminaries on this austere occasion is renewed emphasis on Sentinel as a real activity that FDA is going to undertake. I note that in the past drug companies have provided information. So this expansion, I think, from say 400,000 adverse events for drug interaction is miniscule in comparison with the several billion prescriptions that are written every day.

So, is there a connection between your presence here and the other luminaries who are talking about Sentinel as renewed emphasis in Sentinel?

DR. HAMBURG: Absolutely, yes. Sentinel is hugely important to the FDA. And I think to a very wide

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

set of stakeholders in terms of our ability to really much more effectively know what's going on after a drug is approved and is out in the marketplace. You know, as you know from being a former government official, we all think very carefully about how we spend our time. And there was no question in my mind that I wanted to be here to signal, you know, my enthusiasm for this effort, the importance that we put on it in the FDA and in the Department of Health and Human Services more broadly, and to express my sincere and deep appreciation to all of you to be willing to share your time and expertise with us as we shape this important initiative because I think that our ability to do this and do it right will be transformative in terms of how we're able to address very, very vital questions of drug safety.

I think it also is, in fact, a model for how we can do some other things that are very important to FDA and to public health. It will help us move to a new level of expertise and comfort with strategies that deal with large bodies of data -- strategies of data mining, et cetera, which have enormous value, for example, in

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the area of import safety. We are now in a situation where food products and drug products and other medical products are coming in from all over the globe. We can't possibly be inspecting everything that crosses our borders or going into those countries to provide oversight to assure safety and quality. We need to have better strategies for how we target the things of highest risk.

And the kinds of strategies being developed for Sentinel actually can be very valuable in other arenas as well. And I think it's important within the Agency and outside to also have continuing dialogues with people doing different types of work, but using similar sorts of strategies or approaches so that we can continue to learn from each other, continue to make new connections between scientific disciplines and fields of knowledge and learn.

So, you know, this is really, really exciting stuff. And I hope that this workshop will be very productive because we have high hopes and expectations. And I think the American people are counting on all of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

you.

Thank you.

DR. McCLELLAN: Thank you very much.

(Applause)

Peggy, thanks again for your leadership on the Sentinel Initiative, in particular, and all your efforts in support of leading the nation's most important public health agency. At least the one with the most impact and reach. And some really interesting things going on right now.

So, we're going to move straight into Session 1. And I'd like to get the panelists for Session 1 to come up to the podium right now as I take a few minutes to introduce them.

As I mentioned previously, last year FDA issued contracts for several Sentinel-related projects. And today we're going to hear about the results from three of those projects. Anyone who wants to see the full reports can find them at FDA's Sentinel Initiative webpage.

So, we're going to hear today from Kristen

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Rosati from Coppersmith Schermer & Brockelman, PLC. She's going to present an analysis of legal issues related to structuring FDA's Sentinel Initiative activities.

Then Jeff Brown from Harvard Medical School and the Harvard Pilgrim Health Care Institute is going to talk about potential database models to actually implement the Sentinel Initiative empirically.

And then Jennifer Nelson from Group Health Research Institute and the School of Public Health at the University of Washington is going to discuss some of the methods for safety signal identification and how those methods might work for the Sentinel Initiative. We're going to hear remarks for a few minutes, take a few questions from each of the panelists as we go, so be thinking of those and be ready to come up as we go along. And we have a lot of ground to cover. So let me turn it right over to Kristen.

MS. ROSATI: Thank you.

Well, good morning, everyone. I hope I save my voice here.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

It's really a pleasure to be involved in this event and in the dialogue ongoing about creating a Sentinel Initiative. It's really a significant step forward in drug safety as Commissioner Hamburg just talked about. And it also poses some really interesting legal issues that are really -- we're really in uncharted territory in many ways. So it's really a lot of fun for a lawyer to be involved in these issues.

On behalf of eHealth Initiative under contract with the FDA, I was asked to analyze some of the significant legal issues facing data sources that will be participating in the Sentinel Initiative. So in the next 15 minutes, I'm going to give you a very quick tour through an 83-page single lined report and hopefully will do justice to some of the fairly complicated legal issues that data sources will face in participating in the Sentinel Initiative. We'll then have 10 minutes for questions after my prepared remarks. And then there's also a panel, as Mark mentioned this afternoon, on privacy issues where you'll be able to delve in more detail into that issue.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So our report covers four major categories of legal issues facing data sources participating in Sentinel. First of all, we looked at the Food and Drug Administration Amendments Act of 2007 as the source document that got this going. Then we looked at both federal and state privacy compliance issues, human subject research compliance issues, and then finally tort liability for failure to warn.

One thing we did not talk about is the FDA's legal issues that it will need to tackle in structuring and participating in the Sentinel Initiative, including when and how it will contract with the data sources and other qualified entities that will be assisting with the data analysis.

So, our analysis resulted in a number of recommendations which I'm going to touch on throughout the next 15 minutes and then display them again at the end here.

Now, in analyzing the different legal issues posed to data sources participating in the Sentinel Initiative, it's important to keep in mind that the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Sentinel Initiative will evolve in different phases. The first phase of Sentinel will purely involve data sources keeping the data -- keeping the individually identifiable health information at the data source while they're conducting analysis on behalf of the FDA and its partners. So, no individually identifiable health information in the first phase will be going to the FDA.

Now, it's very important also to look at what happens in subsequent phases of the Sentinel Initiative because undoubtedly as this initiative evolves, it'll be necessary for some individual information to go to the FDA or its partners that are involved in the analysis for a couple of reasons. One is that there are lots of data sources out there in the health care industry, especially as hospitals and physicians migrate to the use of electronic health records, who will not themselves have the bioinformatics experience to do drug safety analysis. And I'm sure they would like to participate in the Sentinel Initiative at some point.

It's also important from a scientific perspective, as you'll hear about -- I'm sure throughout

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the day -- that to the extent that we can have some individual information travel to the entities that are doing drug safety analysis, it makes the conclusions more scientifically rigorous if you can link individual data across data sources and over time.

As you all are aware from your own experience, we all see lots of different physicians, hospitals, and sometimes we're even covered by different health insurance companies over time. And so we will get a better Sentinel Initiative over time if we can link individual data across those data sources. Of course, paying extremely detailed attention to privacy issues.

So turning first to the FDAAA, we concluded that although the statute would prohibit the release of individually identifiable information in the drug safety analysis results, there is nothing in the statute that would prohibit the data sources from providing individual information to the FDA or its partners who will be involved in the drug safety analysis. So this is important because the statute itself would not

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

prohibit the development of the Sentinel Initiative throughout the different phases of the project.

Now let's turn to privacy. This is one of the most significant legal and policy issues as Commissioner Hamburg had talked about in structuring the Sentinel Initiative. The decisions about how individual information is used for the Sentinel Initiative; who gains access to that individual information and for what purpose will be subject to much scrutiny, and appropriately so. Detailed attention to the privacy and security of individual health information is essential to the public trust in developing the Sentinel Initiative. And public trust is built through transparency about how that health information will be used. As Dr. Hamburg talked about, involving the public in discussion about how their health information will be used and having rigorous policies for the protection of information used in the Sentinel Initiative. So I was very gratified to see that the FDA is spending resources to talk about and really grapple with the challenging privacy issues ahead of us.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

FDAAA directed the GAO to evaluate the privacy and security of issues related to handling data within Sentinel. And the GAO issued a report in June of 2009. They had a number of specific recommendations, which I'm not going to talk about. But they did more generally recommend that the FDA develop a plan with milestones -- with specific milestones for addressing the privacy and security challenges. So I'm sure that's one of the things that will result from these public fora that they're hosting and that Brookings is hosting here.

One of the questions earlier today was how does this connect with the health information exchange environment and the development of electronic health records. I'm involved in that world as well and it's very interesting to see that many of these privacy issues are really being grappled with in the health information exchange environment. Because as we move away from using health information just for the treatment of a particular individual to so-called secondary uses of health information -- use of health

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

information databases for public health purposes and for research purposes -- there's a lot of discussion and debate going on across the country in the context of developing the National Health Information Network and Regional Health Information Exchanges.

So the issues presented are very similar, and I think the FDA in its collaborative partners in all of you here really have the opportunity to be really thought leaders that will help not just the development of Sentinel Initiative, but also the development of health information exchange across the country as well.

So moving to particular privacy issues, we looked at both federal and state privacy issues. HIPAA is obviously the thousand pound gorilla, especially after the High-Tech Act, which was part of (inaudible) back in February because it applies HIPAA to what are called HIPAA business associates. Basically, contractors and vendors that serve health care providers and health insurance companies. And High-Tech also vastly increased the enforcement authority and the penalties available. So, if the health care industry

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

wasn't paying attention to HIPAA before -- and I think it was -- they certainly are doing so now. So HIPAA will be a major driver in dealing with handling privacy issues in the development of Sentinel.

Now, generally HIPAA requires individual authorization, also known as consent, to use health information or to disclose it to outside third parties. Here in the context of drug safety surveillance it won't be possible to get individual consent to utilize their health information for Sentinel or other drug safety surveillance programs. And that is because the data sources that will be participating hold data on hundreds of thousands, if not millions of people. And so it won't be practical or feasible, nor do we have the resources to see individual consent.

That makes the privacy protection issues that much more compelling because we'll need to make sure that there's public involvement in deciding how it's appropriate to use that health information. And thankfully, once we do that, HIPAA itself will not be a barrier to the development in the Sentinel Initiative

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

because there's a variety of rules within HIPAA that permit the use and disclosure of health information for purposes other than individual's treatment.

We can de-identify that data, which will be done in Phase One of the Sentinel where the data sources will be doing an analysis and then transmitting de-identified aggregated information to the FDA and its partners for analysis. It's also possible to create what's called a limited data set which is partially de-identified data. HIPAA permits the disclosure of individual health information to the FDA for public health purposes. Obviously, that's a good rule to use in this circumstance. And it also permits disclosure of health information for research purposes, which we'll talk about in a moment. With the approval of an institutional review board, really an ethics board that will determine whether sufficient protection is in place the individuals whose information will be utilized.

Now, there's other federal laws as well that are relevant. There's the Federal Substance Abuse Treatment regulations called the Part Two regulations,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

which govern any information that identifies an individual as a substance abuser. So given how the Sentinel Initiative will be structured, it's very unlikely that these regulations will be implicated.

There's also Medicare Part D regulations, which govern how CMS will participate in the Sentinel Initiative. There's the Federal Privacy Act, which governs federal agency. And it looks a lot like HIPAA for federal agencies.

And then finally, there's the Federal Freedom of Information Act. In the public forum last December, one of the questions was raised by the audience about if my health information is transmitted to the FDA, will someone else be able to get access to that information through the Freedom of Information Act through a FOIA request. And thankfully, the answer is no. There's a good exception to FOIA where medical information or their private information does not have to be disclosed by an Agency.

So, as long as the agency has good policies in place to protect the privacy and the security of any

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

information they do receive about individuals in Sentinel, there is no ability for outsiders to get access to that information from the FDA.

Now, we also looked at state medical record confidentiality issues in our report. And state laws are an area of substantial uncertainty here because there's little uniformity across the country. These laws vary a lot by the types of information that we're dealing with. Most states have special information lines on genetic information, communicable diseases and HIV information. And other types of sensitive information. And sometimes those laws vary by regulated entity as well.

We found that in general, most state laws do support the use of health information for public health purposes and research. So hopefully, in most circumstances, the state laws will not be a barrier to the development of the Sentinel Initiative.

Now, moving from privacy to human subject research protection laws, I'm going to touch just briefly on this. What we looked at is whether the use

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of health information by the FDA and its partners for drug safety analysis is public health surveillance or whether it constitutes research. And we found that the distinction between the two is fairly thin because of the types of scientific analysis that's being used to produce drug analysis results.

So, we recommend that the FDA and the Office for Human Research Protection develop more specific guidance for the data sources on when their use of health information is. Drug safety surveillance, public health activities, and when it is research that's subject to some of these other laws.

I'm not going to touch on the other human subject research compliance issues because we don't have time in these 15 minutes, but the presorts talks about these issues in really substantial detail, including the need for an institutional review board approval if it is research.

One of our other recommendations on this point is that if a fair portion of activities constitute research, it would really be a good idea to develop a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

central institutional review board at the national level to support data sources who are doing the drug safety research so that we could convene groups of people that have a lot of experience in drug safety analysis so that we can have good, rigorous protection of individuals whose information is being used in that research.

Now, the final legal issue that we looked at was tort liability for failure to warn patients. As you'll hear about today, there is a gray zone in drug safety surveillance between when the first drug safety signal presents itself and during that period of analysis when the drug safety signal is either confirmed or refuted to be valid.

So during this analysis period, entities that are doing drug safety analysis are concerned about some of the liability issues that may be presented. When they first find out about a potential drug safety event, there's a potential for tort liability at the state level for failure to warn patients and physicians about the new information they may have found about a drug safety event.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

On the other hand, if they jump the gun and report drug safety problems that are not confirmed through further scientific analysis. They also face kind of a competing liability of potentially defaming a good commercial product. And then also it may be bad public policy because if that drug safety problem is not confirmed through analysis, it scares a lot of people who may have therapeutic value for taking a drug that is on the market.

So this grey zone period has the potential for liability to data sources. And one of the reasons for concern here is that tort liability is dealt with case by case in state courts, and each state court may use -- may come to different conclusions about that issue, even if they are dealing with some of the same public policy items that they will balance to determine whether there should be liability, which could include how serious a drug safety signal was, what the potential harm is to the patient for failing to report to the patient or the patient's physician about the drug safety problem, and then some global systemic issues that we

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

just mentioned in terms of not scaring the public when it's not warranted.

So our recommendations on that point was that it would be very useful for data sources to have model policies and procedures from the FDA to determine when it is appropriate and to whom it is appropriate to report drug safety findings. And ideally, for some type of limited statutory immunity for following those FDA model procedures so that data sources participating in Sentinel and other private drug safety analysis projects can be assured that those scientific -- that scientific analysis does not subject the entities to further liability.

This is just a summary of the recommendations that I just covered in detail there. And I think with that we can entertain some questions.

DR. McCLELLAN: Kristen, thank you. We have time for a couple of questions if anyone wants to make their way to the microphone. And while that's happening, Kristen, you covered a lot of law and regulation in a very limited period of time. Thank you

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

for that.

One of the issues you brought up was recommending that also human research protections and FDA think together about some more clear lines as to what's research and what's public health surveillance. Any guidance for them or thoughts based on what you've seen about how that should be sorted out?

MS. ROSATI: It's interesting because there's guidance all over the place. Right now the office for Human Research Protections has issued guidance on the distinction between quality assurance activities and research, but hasn't tackled the public health surveillance issue. I think the CDC has done some useful thinking on this. And pulling some of those guidance documents together it looks like one of the keys to determining the distinction between public health surveillance -- public health activities and research -- is whether the activity actually seeks to analyze the cause of the drug -- adverse drug event that's observed versus just reporting that it happened.

DR. McCLELLAN: The association. I see.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Okay. Two questions. Here and here.

DR. KRAMER: Hi. Judith Kramer from Duke University.

MS. ROSATI: Hi, Judy.

DR. KRAMER: Hi, Kristen.

I actually was very interested in the same topic that Mark brought up. And it seems to me that if drug device safety surveillance has the purpose of protecting the public from risks from these drugs or devices that it would be illogical to think that surveillance is just collecting the information, but not understanding causative issues that would allow you to appropriately warn. So, could you elaborate a little further on why your assessment was that this distinction between surveillance and research makes sense?

MS. ROSATI: Yes. Thank you for -- and Judy has been active in this area as well in determining what's the distinction between public health surveillance and research. And there's a lot of different ways to approach that.

One of my -- how I approach the issue has

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

more to do with whether the entity handling the information is doing the research versus whether the research is being done. So, for instance, if a data source is just reporting adverse drug events that it observes in response to an FDA query, the entity -- the data source would not be doing research, but it is possible that the recipient of the information would be doing the research because, of course, we need to analyze at some point whether or not a particular drug caused a particular adverse event that's observed. So that's a very good question because one of the things we're doing in looking at the legal issues is the legal issues for whom.

On the other hand, if the data source is the one doing the analysis and trying to determine causation then it is very possible that the data source itself would be doing research which then triggers compliance with these federal human research protection laws.

Did that clarify your point?

DR. KRAMER: Yes. I'm just curious whether the FDA has considered doing research because they're

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

trying to understand causation.

MS. ROSATI: Right. Right. I was asked just to talk about the legal issues from the perspective of the data sources rather than the FDA issues.

DR. McCLELLAN: It sounds like more discussion ahead on that one.

DR. HAAS: Joanna Haas, Genzyme Corporation. Could you comment on what might appear to be an apparent tension between the goal articulated by Commissioner Hamburg to increasing the personalized benefit risk and the privacy issues, particularly since personalizing benefit risk and even the pathway to get there requires often genetic information which can under some circumstances be highly identified?

MS. ROSATI: Right. Excellent question. I think there's a lot of really good work being done on how to minimize the amount of individually identifiable data it will take to achieve the scientific rigor we need to do good drug safety analysis.

For instance, we may at some point integrate genetic information into electronic medical records

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

because it's important for personalized medicine to utilize genetic information. And that information will be very important in determining why a particular drug caused a particular safety event. But we need to be very careful that if that information is utilized it's not connected with that individual to the extent that it's possible. And again, to have really, really rigorous privacy and security policies surrounding who can access that information and for what purpose. Obviously, we need to really limit the number of people that would see any individually identifiable health information, particularly genetic information. But at the same time balancing that against the real -- the public good that can come from harnessing this amazing wealth of information that we'll be able to develop through electronic health records and the development of health information exchanges.

But you've gotten to exactly the public policy issue that we're all going to be struggling with in developing this great resources.

DR. McCLELLAN: It sounds like more work

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

ahead on that one, too. Kristen, thank you very much.

(Applause)

And we can move on to Jeff Brown.

DR. BROWN: So as the slides are coming up, I mean, this is -- it's a great panel because actually my day job is to try to figure out systems that meet the requirements of people on my left and on my right, basically. So the scientists are telling me what they need, but then the on the legal side they say, well, wait a second. I don't know what we can do there. So it's really -- I don't know, I thought I was getting away from the office, but this is actually what I'm doing every day -- is trying to develop this system that fits within those boxes.

So I'm going to be talking about -- this is a report we did with FDA. I'm going to really try to focus on the recommendations, thinking about what we call the database model. We can think about it as a system. This is the report and it was completed in May and it's available.

So, the objectives of the report are

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

relatively straightforward. It was, step one, describe the user needs. What does Sentinel need to do? Step two, think about the database models that are out there. We really thought of them separately. Then, Step three.

So I'm going to take a step back. Database models is not data resources. We weren't thinking about what kind of data -- who has the data. It's how is the data organized is really what we're thinking. Step Three was let's compare and contrast those things. Four, go out there and look around the country, actually around the world, to see what's been done in this realm. I'm actually not going to report much on that just in the interest of time. And then five is kind of thinking about the recommendations.

So what we ended up doing was to try to organize the report based on these five questions. It's almost a decision tree. There's a little bit of a circular logic in it so it doesn't work great, but we had to kind of push ourselves through it.

So what does the system need to do? What data are needed to do it? Where will the data be

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

stored? So I'll take a step back and say within Sentinel there's an assumption that there's no single data source that can handle everything we need, so now we're talking about multiple institutions. Multiple health insurers, electronic medical record systems, wherever they are, but there's no one place to go. So we're talking about multiple places.

Now we have to think of where are the data going to be stored. Once you make that decision you have to think about how you're going to analyze it and then there's an issue of a common data model which leads from the decisions you make on the previous questions.

So what does the system need to do? We went out and we talked to the FDA medical centers. We talked to federal partners -- CDC, NIH, AHRQ. What would you do if this Sentinel appeared tomorrow? What would you want this thing to do? And then we talked to stakeholders. We talked to the public. We actually took the list from the previous public meeting and kind of laid out a framework and said what do you think just to get feedback on what other people would want the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

system to do. You can imagine the answers were just about everything.

I'm focusing on the primary uses, which means the FDA's uses. And these obviously aren't all of the ones even that FDA came up with, but it's relative -- it should get us going. I mean, adverse event surveillance is obvious. Confirmatory safety studies, pretty straight forward. We got a lot of discussion about just adoption and fusion of new technologies. Who's using it? How is it out there in the public? Just to understand that was an important need from the medical centers. The augmenting registry information actually turned up because a lot of the device information is sitting in registries and we'd like to add information to those registries to make them a little bit more useful.

Calculating background rates was mentioned by everyone, particularly at FDA. We just need to know what we'd expect out there day-to-day. What's the rate of this in the population of teenagers and adults? Whatever it would happen to be it's actually not easy

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

information to get to, but we should be able to get to it quickly because it really helps FDA think about the information that comes in the door every day.

We wanted to use the Sentinel system to understand how to use the Sentinel system is really what this bullet point is. To understand how to use electronic data to do this kind of work. We're pretty comfortable in understanding it, but we can do better. What algorithms work and what don't? We really have to understand what it's good for. What these data are good for, what those data are good for, and what they're not.

And then there's all these other potential uses. You can use the same kind of data that we're talking about to do comparative effectiveness work. You can do disease surveillance. You can do quality work. You can do lots of interesting things with that kind of data, but it's not really one of the primary uses as we were thinking about it.

So now that we really know what we need from Sentinel, what data do you need? And it's actually relatively straightforward. You need to know just

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

really a couple of things. You need to know an exposure. Took a drug on a date or something was inserted. It was a knee replacement on a date or a vaccination and a date. And then you need to know an outcome and a date. An outcome and co-morbidity are often the same thing just depending on what you're studying, so they're there together. And then because we're talking mostly about insurance information, enrollment dates are important and then demographics. It's actually not terribly complicated. We can do a lot of work. An awful lot of work with just this kind of minimal amount of information.

Some additional things that we'd like to have are being able to link across datasets. And I'll talk about it again, but think about it as cross sectional linkage and longitudinal linkage. And more clinical detail. You'd always want more clinical detail. That's what the people on my right are always asking for. More clinical detail to improve the work you're doing.

You know, and I have full text medical records here and I'm not exactly sure whether it should

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

be there or above. In the report we had it as kind of listed as it is. But it's important to be able to go and validate outcomes for a lot of the things we're going to want to do within Sentinel. Not everything, but a lot of the things.

So, the point is really that there's not a lot of data elements that you need for most uses. And we should make clear that the needs for Sentinel are distinct from the needs of a health insurer to pay claims every day. And they are distinct from the needs of a health care system to deliver care. They are different than the needs of, for example, health information exchange or even a medical system where they're trying to improve care at the point of care for that patient at that time. That's not the need of Sentinel.

So we ended up really -- it probably won't be much of a surprise thinking about claims data will end up being the most important. Claims linked with EMR is really -- would be fantastic. It's just that doesn't exist for very many people in the country. It's too

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

bad, but that's just the way it is. So the recommendation -- and all my recommendations will be initially focused because this is a system that will be built over time and can be improved over time, but it's initially focused on health insurance claims data -- we call it administrative and claims data -- for a defined population. Think about insurance claims. That's really the focus -- the initial focus of Sentinel.

So now that we know what data we need, where are you going to put it? It's a pretty important question. Remember, we have to go to multiple institutions to do this so we have to decide whether there's a big centralized data warehouse or we're going to use a distributed approach where the data holders maintain physical control of the data, which implies they also control all the uses of the data. So our recommendation is a distributed model for a lot of reasons. Data holders really want to maintain physical control of their data. It also keeps the experts -- the data and the experts next to each other. The data sources are hard to use and the people who know the data

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

best are actually going to control access to it. And you have their expertise.

So, now if we're going to have a distributed model -- remember, we kind of figured out what Sentinel is going to do; what data are needed; where you're going to store the data. You have to make that decision. If we decide it's distributed, whether health plans or the data holders hold it, you have to figure out how you're going to analyze it. This is very much the pragmatic decisions you have to make.

There are really two options. You can have a single -- I don't think this is too technical -- a single, analytic program that you basically send to the data holders and have them execute against their data resource. In order to do that there needs to be a common model. And I'll get to that in a second. Or you can send to the data holders basically what would look like a research protocol and say implement this research protocol and send us back the information. To do the second, each individual data holder would have to have basically an analyst -- kind of an investigator and an

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

analyst doing programming locally to implement a protocol versus the first option which is a single program that goes out and executes against the data sets the same program.

Our recommendation was a single, analytic program. And it really just ensures the complex analytics are done identically. There's really no other way to ensure that the complex analytics are done identically. Simple queries aren't really what I'm worried about. I'm worried about when you really want to do a complex study. If the people in the room have tried to do it, it's very hard to imagine a way to duplicate that study in silos. You really have to do it one time and have it execute identically.

So if you're going to do that, meaning send one analytic program, you need accommodative (inaudible). It is really the way you have to go to make it work. So what do I mean by that? It's really not terribly complicated. You have to have the data that sit at the data holders all look the same so the same program -- analytic program -- can run. At some

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

level it's as simple as making sure the variable age is spelled the same everywhere or sex isn't sex one place and gender somewhere else because the program won't work if that's the case. And it gets to be a little more specific after that.

You can implement a common data model either physically or virtually. The virtual transformations actually get a little complicated. The physical one, essentially what I'm saying is an insurance company. I sit inside Harvard Pilgrim Health Care, an insurance company. We could basically make a copy of our data and have it sit in the common data model so when we get a question or a query I can just run it against it.

So the recommendation is for a physical implementation for all or a portion. The reason I say a portion is because there are people in the room that have very large data sets and they're not going to want to make a copy of it. So we can -- there's a way to handle it so that you don't have to make a copy of very large data systems. At Harvard Pilgrim, I have a million members. It's not a burden for me to make a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

copy of the data. For a very large system it would be a burden and there's a way around that, partly by doing portions of the population and relatively other simple approaches.

So types of models. This is this question of how are you organizing the data. These are listed in order of granularity. This is kind of decreasing granularity. The top -- the top one is -- basically think about it at a claims level. It's a record for every time someone shows up at a medical facility. It's what a big claims database basically looks like -- encounter level. And then you can have different ways of organizing the data. So the second one is just a way of kind of instead of seeing 15 diagnoses of diabetes you might say this person had diabetes from this date to this date and just kind of link them altogether. Just a different way of thinking about it.

And then it goes all the way down to summary data which might just be how many people took this drug last year. There's no PHI there at all. Which one do you choose? It depends on the question. The answer is

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

always going to be "it depends." So, for adoption and effusion , you can actually have summary level data for most of the work and do just fine, but it won't really work for active surveillance. So that's kind of those tradeoffs.

There's obviously a lot of variance to how to organize the data. And it will always be what's the question. The rule is you really want to have -- you only want the detail that you need to answer the question basically is how we try to think about it. And there's obviously a lot of ways. I want to make sure I just note there's a lot of ways to enhance the value of the data through common terminologies. We haven't forgotten there's all this work going on in the country about terminologies and medical terminologies. You can use all those things to make these work a little better.

So, these are a couple just things that we have to think about when you're considering the data model and the kinds of data. Most of these have to do with linkages. So there's linkages to medical charts. It's actually really important to be able to do it -- to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

validate an outcome. Did that really happen?

Particularly if we're worried about something that's very rare. You probably need to know whether it's a birth outcome. They might not see very many and one or two moving one way or another will change your findings.

There's linkages to external data sources which are here. Think about the national death index or birth registry, cancer registry. Being able to link to those is important. Linkages between institutions. I understand that linkages is scary. Right? But these are the things you have to think about when you're designing the system. So linkages between institutions are cross sectional or longitudinal. And then timeliness of data obviously matters a lot, particularly if you're doing active surveillance.

So, this is an illustration of kind of the system you get based on the answers that we just gave. So, here there are four health plans. They all have their local data organized however they do their local data organization. You ask everyone to create a common model. So they've taken their data and made it

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

basically all look the same. Then the coordinating center will send the question. The question can be in the form of a program. I'm recommending that it's in the form of an actual piece of code that goes out. The health plans -- these data holders then actually review it. What are you asking? Why are you asking it? It's not just kind of going and chugging along. We need to know what's being asked. If they decide to then execute, the health plans would review what comes out of that query and then decide to return it. All of those breakages -- all of those manual steps are important because they're all places for data holders to say no. No because of privacy. No because of a corporate policy. No because of a state regulation. You have to have those abilities to say no. If they meet all those and they decide to send it back to the coordinating center, now we have our information back outside of those plans. Typically, that can be the identified information and then we go off and do our analytics and we're done.

DR. McCLELLAN: Great, Jeff. Thank you for

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that overview. I'm not sure we're completely done, but it does make it sound straightforward.

DR. BROWN: I'm done because Nadia said I'm done.

DR. McCLELLAN: We have time for a question or two if you want to go to the microphones. Yes, go ahead.

SPEAKER: (inaudible). You used the word "outcome" in terms of data. And I'm curious as to whether or not you mean outcome both in terms of risk of morbidity or also do you track efficacy or benefit at the same time? In other words, are you just finding out that if I had lymphoma I had a side effect or are you also finding out that my disease stays in remission?

DR. BROWN: I should really let FDA give the more detailed answer to that. It depends on what the question is.

The reality is it depends on the question. I've done studies where the outcome is seizure as a bad thing or a reduction in seizure where that's a good thing. So, the data can do which -- can handle the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

question. It depends who asks it.

SPEAKER: Okay, but -- okay, thank you.

DR. MARK: Tami Mark with Thomson Reuters.

You mentioned the need to validate outcomes going back to text medical records and that seems like the aspect of the system that would potentially pose the most privacy issues. And as we develop more understanding of the validity of outcomes and claims data, for example, how well can we understand whether a GI event occurred or AMI occurred, not going back to medical records, do you see the need to go back to the medical record as diminishing or do you think we're always going to have to have that aspect of the data there?

DR. BROWN: That's a good question. I think the more we can validate outcomes -- and actually OMOP is doing a lot of work in that area -- the less we'll need to go back. So if we can really -- if we get comfortable that an inpatient primary diagnosis of AMI really isn't AMI, then we won't have to keep going back. So I think there's a good amount of foundational work to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

do those things so that we can do -- kind of do it once, validate it. Of course, all the data change and there's all the extra problems there, but I think it's important to do those things so we don't always have to go back. It's expensive to go back and it's time consuming to go back. Plus all the privacy issues of going back. So we'd rather avoid it.

DR. McCLELLAN: In the meantime, for the initial model you did have some discussion of building in this capacity to go back. Is that something that would be handled by each of the participating data centers or are there different ways to do that, too?

DR. BROWN: Yes. By keeping the data out at the data holders, the way that we typically would work the system is that if we needed to go validate, it would be the data holders going back to the chart. Whoever the chart happens to be. Sometimes the data holders are the same as the provider and then that's pretty simple. Or it's a health insurer going to the hospital and saying we're requesting this chart for this study under these approvals, and can we do an extract? So it's the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

data holders going back and not the coordinating center going out and doing it. But it would be kind of all back behind the firewall. Because, really, all I want to know as a coordinating center is validated yes-no. I don't want any of the -- I don't want any protected information. I just need the outcome of it.

DR. McCLELLAN: Okay. Thank you. I think we have time for one more question in this round and I think you were up next.

MS. SHARFMAN: Anna Sharfman from (inaudible). Thank you.

When you validate the outcomes in the database it will not mean that the same outcomes will be validated in all the other distributed databases because there are some data points that can be critical to get one result to another. Having a common data model will help, but the way that the data was structured and was transformed -- this is from our experience with (inaudible) data standardizing and using automated analytical tools. It can change the whole interpretation. Being able to work together from the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

same data -- in front of the same data facilitates interpretation. How do we decide that the patient had certain conditions? For example, ALS. If you are -- if you don't have ways of representing multi patients and be able to understand that two cases of ALS do not have one code ALS during that period of time, but they have other ancillary codes that will tell you that they are not (inaudible) problems, also. Then there is a need -- it's not linear. That we declare that we have a protocol is not linear, that we know which are the most important issues -- safety issues that we need to analyze. Because from experience we know that we missed some important signals like PTU and acute liver failure for 60 years. Then we need to have multi-patient representation of the data. And to be able to share these multi-patient representation on individual patients.

DR. McCLELLAN: How do you get consistency with all this data?

DR. BROWN: We have to -- basically you have to do the best you can. We have a lot of really smart

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

people who understand the data and understand the systems. It's a secondary use. It is not designed for doing research or surveillance. And really, the people who know the data well will help us identify those pitfalls. The reality is the data are collected to pay providers and to provide care and they're not really worried so much about what we need it for. So we just have to do a good job thinking about it.

But if we try to make it perfect, we won't get there. If we try to get to 100 percent of we're really sure that that means that these 5 codes mean ALS, that answer actually tomorrow might not be valid. And you have to just -- we just have to know that. So we have to be thinking about it and think about how we do our research and ask the right questions as we go along. It's a conflict every day.

DR. McCLELLAN: Jeff, thank you very much.

(Applause)

DR. McCLELLAN: Jennifer, I'm sure you'll cover how all these data challenges can be handled and the methods that work, too. Right?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. NELSON: Well, thanks very much to Dr. McClellan and to the others at Brookings for inviting me to be here today.

I'm very pleased to share with you -- let's see if I can get this to work -- our group's evaluation of existing methods for safety signal identification for the Sentinel Initiative. This is work that we conducted in collaboration with FDA about a year ago.

I'd like to acknowledge my collaborators at Group Health Research Institute and the University of Washington, and also express appreciation for statistical consultants at Harvard Medical School, Harvard Pilgrim Health Care, as well as Lincoln Technologies Division of Face Forward. And also acknowledge the Sentinel Initiative planning contract that funded our work.

So, I'm going to be brief and try to review some very general approaches -- some of the most common general approaches for signal detection and weigh their pros and cons for potential use within Sentinel Initiative. And in the context of weighing these

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

methods I think there are four key aspects of Sentinel that are unique and that bode on which methods -- we want methods that will perform well in the following setting. In particular, Sentinel is interested in observational surveillance of a large and broad population. Interested in surveillance that's proactive, rapid, and done over time versus at a single point in time. So this is the context in which we're thinking about methods and which will do well. And I'll end by briefly discussing how we might begin to implement such methods and identify some of the gaps that exist that we need to overcome.

So, the first major approach that we considered was data mining. And this was a very broad area. We focused -- it involves extracting hidden patterns in large data sets. And for medical product safety surveillance, what this involves is simultaneously evaluating all or very many adverse event and drug pairs for potential associations. And one of the main existing approaches that's used within the general field of data mining are disproportionality

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

analyses. So, basically to give you an idea of what's involved with this type of an approach is for each drug of interest and adverse event of interest you construct a two-by-two table that looks like this. So you're classifying observations as to whether a particular event occurred or not and whether it occurred among those who received a particular drug or not. And then for each of these pairs you use the information in this table to compute a measure of disproportionality. So our events of a particular interest occurring more often among those who received that particular drug. So you do that for every adverse event drug pair and you rank those. And those that have the strongest associations above a particular threshold will be the ones that we'll signal according to this methodology.

So the key features to note of data mining. This is a hypothesis-free study. It's generally been implemented in a retrospective fashion at a single point in time or a few points in time, so we're allowing a lot of data to accumulate before we go ahead and do an analysis like this.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Some of the major applications that exist for data mining in the safety surveillance setting are analyses of the passive spontaneous reports that are collected internationally and nationally by the WHO, their adverse drug reactions databases, FDA's adverse events reporting system, and CDC and FDA's vaccine adverse events reporting databases. These are also common activities performed by Industry as part of their pharmacovigilance.

There have been efforts to conduct feasibility studies of adapting data mining methods to a health care claims setting and a longitudinal setting like we expect to see in Sentinel, but these are relatively preliminary pieces of work at this point in time.

And so data mining methods have shown to have some success in some situations. For instance, the initial Rotavirus vaccine was suspended in 1999 based on data mining analyses of the Vaccine Adverse Event Reporting System's data which found 15 cases of inception among infants who had received this vaccine.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

A second broad class of methods that we evaluated were sequential testing methods. And in contrast to data mining where we're in a land of hypothesis-free, in sequential testing the first thing you do is pre-specify some set -- maybe one or a few targeted pairs that you're interested in. Targeted drug and adverse event pairs. So you might have a specific hypothesis that Vioxx recipients might have an increased risk of MI based on information you saw pre-licensure and you might test that against the null hypothesis that there's no difference between those who received and did not receive Vioxx.

Then the idea behind sequential testing is that as data accrue you analyze the specific targets. And so just to give you an idea of basically an example of what you could do, after a drug is licensed each week you could count up the number of events that occur among those who received the particular drug of interest, count up those events that occur among some comparison group not receiving the drug, compute some statistic that you believe is good at representing the risk

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

difference between the groups of relative risk or a difference in risk. And if that statistic is too large based on some precept threshold that you specify, you'll stop and signal a safety problem.

Alternatively, if you get to the end of your study where you feel like you've accumulated enough information and you have not signaled by that time you would make a conclusion that you have not enough evidence to detect a safety problem.

And a key feature of sequential testing to note is that this too big quantity, this stopping boundary, is explicitly chosen to maintain a certain level of false positive error rejection. So typically studies don't want to see more than five percent of their results occurring on falsely -- when there's really no -- when there's no finding there.

So here's a visual representation of what sequential testing might look like. Say you have a drug that goes to market in December and you could continue with monthly testing on a sequential basis. So, on the vertical axis here we have a fancy statistic that's

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

used to quantify a difference between people who are receiving and not receiving a drug. And you can compute the statistic on a monthly basis. And you can see here in about April, at that test we have exceeded the horizontal flat threshold which would indicate based on this setting that we should stop as we detected an increased risk among those receiving the drug.

So the key features of sequential testing as I hope I've just illuminated are we're now in the realm of formal hypothesis testing. We're doing this work prospectively so we can do it rapidly if we like as data are accruing in time. And we're making repeated tests.

There are actually a wide range of applications that use this approach. It's a very widely used procedure for efficacy monitoring and pre-licensure trials primarily for efficacy, but also some for safety. There have also been -- there's preliminary work that has been done within the context of post-licensure drug safety surveillance to use sequential testing. And this has been done within the HMO Research Network by the Center for Education and Research on Therapeutics.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Sequential testing on a weekly basis has also become a routine part of what the CDC's Vaccine Safety Datalink, VSD, collaboration does to do post-licensure monitoring of vaccine safety. I think it's worth describing a little more detail about what's done within the VSD and what the VSD is.

So the Vaccine Safety Datalink is a collaboration between CDC and eight health plans. And it involves data on about 8.8 million enrollees from those health plans, or about three percent of the population in the U.S. Within each site of the Vaccine Safety Datalink there are data systems on immunization records, adverse events from hospitalizations, emergency department visits, outpatient visits, and patient information demographic characteristic risk factors. And these are linked by a common study ID within that site.

Then, as Jeff was describing, these data are transformed into a common data model that can be accessed by a central coordinating center. So we standardize this information so it can talk to each

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

other across the sites. And this information is now updated on a weekly basis. And this has allowed for routine longitudinal monitoring of new vaccines for safety since about 2005, including most recently H1N1 swine flu vaccine.

And this is also shown to have success in terms of identifying problems more quickly than in prior approaches. In February of 2008, the new combination Measles-Mumps-Rubella, MMR, and varicella vaccine was found to have an increased risk of seizure among infants compared to receiving separate injections of the standard MMR and varicella vaccines. And this was identified first within the Vaccine Safety Datalink active surveillance program.

So what are the pros and cons of these two main approaches? Well, for data mining, as I've demonstrated, it can be a very useful way to glean information and in particular has been shown to do so spontaneous report data systems. However, the control for false-positive rates, in particular, compared to a sequential testing framework is somewhat ad hoc. In

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

addition, associations for a given adverse event and drug pair can be masked in a data mining setting for a variety of reasons, in part due to the sheer magnitude of the multiple testing in all of the information you're looking at. You're kind of dealing with the "needle in the haystack" problem.

In addition, if you've included in your mining procedure drugs that are actually indicated for that adverse event -- so drugs for which you would expect a strong association -- that can potentially bury other associations that you may be interested in trying to find.

In addition, the existing data mining methods are primarily designed for a retrospective, single, one-time analysis and so it's not -- at least it's not initially immediately clear if or how you might want to begin to apply such methods prospectively, although work is being actively done in this area.

Pros and cons of sequential testing. So this is an established methodology as I mentioned for monitoring efficacy in randomized clinical trials often

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

done pre-licensure and sometimes post-licensure. A special case of sequential testing has proven successful for active surveillance within the Vaccine Safety Datalink, and this is weekly surveillance using a flat stopping boundary that I showed you in that picture before. But there are other monitoring approaches that can be considered so it really offers a nice, flexible monitoring plan framework. We can vary how often we perform the testing, and we can vary the shape of that boundary depending on the tradeoff that we desire between how fast we want to detect a problem and how powerful we want the approach to be and how we feel about making false-positive mistakes.

However, despite the fact that this is widely used for efficacy in clinical trials in particular, there's not as much information to guide choices about how to use these methods in the safety setting. And so questions about the optimal design are just being studied now. How frequently should we perform testing? What shape of stopping boundary is most desirable? And questions like this.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

I think it's worth describing, in particular, some of the pros and cons of the approach used within the Vaccine Safety Datalink project which involves near continuous -- so weekly testing -- and a flat boundary. So highly frequent testing is a good thing because we can find problems sooner on average than if we look less frequently. However, highly frequent testing may not be feasible in all settings and Sentinel may be case where it's feasible; it may be a case where it's not feasible. There's a lot of infrastructure required to do testing on a very frequent basis.

It's also a potential that you will sacrifice data quality the more frequent you look. Inherently you have less time to look at your data than if you waited longer between looks and had a chance to sort of process data even more. It's less powerful than if you test on a less frequent basis. So the more frequently you look, the more you have to guard against false-positive errors occurring. And so you need to raise your threshold up and that causes you to have a less powerful design.

And it may not be necessary to look very,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

very frequently. Most of the problems that we want to detect post-licensure are going to be the things that we didn't think we found pre-licensure. So they may be quite rare; they may not accumulate very quickly. We may not need to look that often. We clearly want to look routinely though.

The other aspect of the VSD approach has to do with the boundary selection. So a flat boundary is used. And that's in contrast to what's typically done in sequential testing settings for clinical trials and efficacy where a very high boundary is used early on that decreases later in time. So a flat boundary is a good thing because you're more powerful earlier on. You can find problems at earlier time points, but you also may make false-positive errors at those earlier time points when you have a little bit less data and there's more variability and uncertainty in those data. A flat boundary is also less powerful overall than other boundary choices.

So now I want to step back a little bit from these two major approaches and talk about a third thing

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that we did in our contract, which was begin to try to propose an implementation strategy that involves some of these methods and how would you go about doing that. So this is just one possible approach -- an initial idea. And there may be many. But I think most would agree that the first key step in conducting surveillance post-licensure is to start with what you know and perform a comprehensive and conflict review of all phases of available pre-licensure data.

Secondly, take that information and develop an approach to identify and prioritize what target pairs are going to make sense for a proactive post-licensure safety surveillance like Sentinel wants to do. There may be other -- there are other mechanisms and there may be other systems besides Sentinel. And so you want to ask questions such as are the data of adequate quality to support surveillance? And what is the size of the risk you want to rule out? In other words, which are the pairs that are most conducive to successful surveillance in a Sentinel-type setting.

Thirdly, we'd recommend as a primary approach

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to surveillance formally and sequentially testing these target hypotheses as opposed to an all-by-all data mining approach as we think this will be more efficient to focus on the most important and potentially most reliably measured adverse event drug pairs. Sequential testing also explicitly controls for false-positive error rates, and I think it's important to minimize false-positive errors in the context of Sentinel where it may be very expensive to follow up on errors like this.

Fourth, testing is not enough. There's clearly a lot more that needs to be done to inform the results of those tests. Data quality checking is inherently important. Risk estimation that quantifies how big the problem is once you see it. So it's not enough to know that there is a problem, but how big is the problem. So does it matter? And then follow-up studies that confirm the initial findings.

Finally, the last two recommendations have to do with the fact that there's clearly not one method that's going to find everything and give us all the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

answers, so we need to be doing complimentary approaches and looking at complimentary data sets in addition to Sentinel. So keep doing the good things that we're already doing while we get the Sentinel Initiative up and running.

And so finally I just want to close -- I'm not going to walk through this slide in detail, but just wanted to identify some of the methodological gaps and the future work that is needed that I think is important to ensure a more successful Sentinel Initiative. And the main message of this slide is just to say that we have a lot of work to do across a wide variety of areas. We would like methods to improve the way -- the data accuracy of the information we're using. There's a lot of technical advances that are going to be important, both in the sequential testing realm as well as data mining. It'd be great to have a better framework to evaluate how well these methods are doing, as well as better methods to assess to the robustness of the signals that we do detect.

And these are exactly the missing pieces of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the puzzle that FDA is addressing with ongoing projects. And I'm very honored to be a small part of those efforts.

Thanks very much. (Applause)

DR. McCLELLAN: Jennifer, thank you.

Looking at the clock, we have time for one or two quick questions. If there are any, please head to a microphone.

Go ahead.

MR. NYE: Hi. This is Vinnett Nye from Humana.

First of all, thank you for that wonderful speech. Having had -- what do you call it -- painful pleasure of working on the OMOP a lot of these things are becoming, you know, more and more clear. It's just not as straightforward. I think Jeff put it very candidly as to create different (inaudible) models and, you know, pitch the research sources against them.

I was wondering, one of the key questions that keeps coming to my mind is our ability to define a lot of these things as we implement them. And my

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

question is particularly for -- if you're trying to find out adverse drug reactions, first of all, are we going to define adverse drug reactions, one. And two, in the context of medication errors, there could be adverse events that are caused by medication errors. So is there any thought process behind delineating adverse drug reactions towards medication errors in (inaudible)? Thank you.

DR. McCLELLAN: Adverse drug reactions versus medication errors as the cause for the association (inaudible).

DR. NELSON: I think -- yeah, as Jeff was describing, any data that's collected not for the primary purposes of research is going to have to be carefully scrutinized before you sort of input it into some method that tells you if there's a signal there. You really need to look at -- once -- if you have a signal -- it would be great before you have a signal to be defining your outcomes and defining your drugs in ways that you are comfortable with the validity of those measures so that when you do get a signal you feel like

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

you can trust it. But, as Jeff said, you can't do it all at once either. You need to provide some reasonable definitions for those things, move forward with some sort of methodology to see if a signal is there, and then take several steps after that to validate is the signal occurring across multiple sites that would make you feel more comfortable that it's something that is real.

So, there's data quality. I think the issues you're raising have to do with data quality and you have to be cognizant of that through all the steps of signal detection, strengthening, and confirmation.

DR. McCLELLAN: Another example of iterative processes to get to better methods and data systems.

Bruce, last question.

DR. SMITH: Yes. Just a question. Bruce Smith, Brookings.

The relationship you alluded briefly to -- pre-market testing and the original approval -- if you look at efficacy in safety and drugs, what is actually the connection a little bit between the kind and degree

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and magnitude of the initial review in the clinical trial and actually what you do then in the post-market? Could you expand on that a little bit?

DR. NELSON: Sure. So in pre-licensure, the key features of a pre-licensure study are, as I think was mentioned earlier, we have a fairly select population, a relatively smaller population, and a very controlled setting. And so we can't possibly find everything we need to find in those settings. In particular, what's done in terms of adverse event reporting is to try to describe what's there and there's events that are going to be too rare to be found in those settings. And so I think the focus of post-licensure studies is -- and the advantage of having post-licensure studies is a much broader population, larger numbers, and the ability to find problems that you couldn't possibly find.

DR. McCLELLAN: Thanks again. (Applause)

Another round for the whole panel. They covered a lot of ground in a small amount of time. Again, the detailed reports are available on the FDA

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Sentinel website. And I'm sure they'd be happy to discuss further issues with you. But you're going to have to do it briefly if you want to do it during this break. We're running just a few minutes late. I'd still like to get back to work as close to 11:05 as possible. So if you're going to get up and get moving, go ahead.

Our next session will start as close to 11:05 as we can. It's on an update on FDA's current medical product safety initiatives. And our research director, Josh Benner, will be moderating that panel.

Thank you all very much.

(Recess)

DR. BENNER: Josh Benner with the Engelberg Center. And it's my pleasure to resume our workshop with Session II. These will be presentations and discussions of what is happening with the Sentinel Initiative and other safety surveillance activities at FDA as we speak. So already a number of you have been coming up to us at the breaks asking, "But what's happening today in safety surveillance?" And so this is

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the session that will begin to answer those questions for you.

Dr. Janet Woodcock, the director of the Center for Drugs at FDA is going to provide an overview of FDA's current safety initiatives. Then we'll hear from Patrick Ryan, who is a drug development scientist with GlaxoSmithKline and a co-investigator on the Observational Medical Outcomes Partnership to provide an overview of that project. Finally, Dr. Rich Platt, a professor of medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute will summarize his team's work on a new FDA contract to build an active surveillance data network and coordinating center.

After all three presentations are complete, we'll have time for questions and comments. So I'll ask you to hold your questions and comments until the end of all three presentations.

Janet?

DR. WOODCOCK: Thank you very much, Josh.

I'd first like to thank Brookings, Mark McClellan, Josh Benner, and Sally Cluchey for their

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

partnership in helping us, especially with these public meetings that we're having to advance Sentinel. I'd also like to thank the FDA Sentinel team, especially our chief counsel, who has really never once said to us, "You want to do what?" That's very refreshing. And thank all of you, the many others who have been working on this, some of which you've just heard from.

Now, I'm going to step back a little bit and look at the big picture of medical product and drug safety, but first I want to go through kind of the big picture of where Sentinel fits within all of this. Sentinel is really an idea whose time has come, but like most such ideas it's been a long time coming. And I guess during the break you have been hearing, well, when is it really coming?

The history is in 2005, HHS and FDA begin discussions of using eHealth data more systematically for routine drug safety surveillance. We certainly had been going with studies -- pharmacoepi studies within eHealth data for a long time, but we hadn't had the thought of setting up a routine system. In 2007, as you

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

heard, these thoughts were codified in the FDA Amendments Act. And in May of '08, we actually launched the Sentinel Initiative. So it really hasn't been that long.

The basic premise is that with extensive use of pharmaceuticals and health care we need a much more real-time safety surveillance system to augment the current -- I think it's fairly described as a patchwork of voluntary reporting, post-market studies, and clinical reports that we currently deal with. Increasing availability of eHealth data out there, which is an Administration priority, really has provided a new opportunity that we expect to grow significantly over the next several years.

But, of course, it is not easy. And you've heard this already and you'll hear that today more. There are multiple challenges, including the fact that eHealth data is not standardized and exists in all sorts of formats. And we don't know how valid our codes that we're looking at are or even descriptions in the records sometimes. The fact that consensus methods for

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

analyzing these data and grouping the data do not necessarily exist. And you've already heard some discussions about the analysis of different ways that might be done. And the need to query such data while rigorously protecting privacy and ensuring data security.

So these are some of the central challenges that face us as we move forward. And FDA has been methodically addressing each of these issues as we build the groundwork for the large Sentinel system. We've led a series of contracts on privacy, security, governance, and related matters, as well as methodologies. We're working in multiple collaborations on the science. You're going to hear about the Observational Medical Outcomes Pilot, or OMOP, from one of the PIs. This is a partnership amongst FNIH, the Foundation for NIH, FDA, and PhRMA. This isn't doing analyses to find new signals; this is testing methodologies. How do you create such an infrastructure? How do you govern it? How do you do -- what are the methods that might be used to perform analyses?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And I think Patrick Ryan is going to give you a much more comprehensive description of what's going on there. But OMOP has already, for example, created a common data model and is evaluating methods. And I've already heard from other researchers in the field that they are starting to use the public -- now publicly available information that's being posted by OMOP as they devise their research approaches. So I think that's a very positive step.

We also have been doing a lot of work in the federal government. You've heard about the Vaccine Safety Datalink that's been going on. Also, AHRQ has been funding for many years some type of this work. At the beginning of Sentinel, FDA created the Federal Partners Working Group. This is a test for all of you of federal acronyms. This includes FDA, ONC -- that's the Office of National Coordinator -- NIH, CDC, CMS, DOD, VA, HRQ, IHS -- that's the Indian Health Service -- HSRA -- Health Services Research Administration -- OHRP, which we've already discussed earlier and obviously is a key player, and the Consumer Product Safety Commission,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

also known as CPSC. Okay?

So we've brought -- we discussed amongst all these parties all the various issues, many whom each have a piece ---- a role to play, or some of whom have major research programs or are holders of large electronic data sets.

We also have the Safe Rx Collaboration with CMS. And here we're testing the ability to do near real-time active surveillance using the Medicare Part D data. And this would be somewhat similar to what was described for the Vaccine Safety Datalink. And these methods -- of course, Part D is still very new -- and these methods are in development. But this is a resource within the federal government that CMS is collaborating with FDA on. We're also collaborating with the Department of Defense and the VA specifically on their electronic data that they have. And they also perform some quality and safety surveillance already on their populations.

In addition, this is not just about the United States. Okay? Internationally there's also a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

lot going on, although people around the world are looking with great interest at Sentinel and what we're going to do here. In Europe there's a European network of Centers for Pharmacoepidemiology and Pharmacovigilance. They form a network of excellence. The Innovative Medicines Initiative, or IMI, is going on in Europe. And Topic 6 of the IMI is the Protect Initiative. And the IMI projects are half-funded by the government -- by E.U. -- and half-funded by private sector. So they're public-private partnerships. And Protect is intended to look at tools and methods for pharmacovigilance and pharmacoepidemiology, and the EMEA is involved in this. So we're watching that carefully and we'll be sharing information with that collaboration.

And in the E.U., they also are working on better computerized methods for adverse drug reaction repositories. In Canada, they have a Drug Safety Effectiveness Network, or DSEN. And that's linking researchers around in Canada. And in Asia and Japan they're having similar thoughts and directions about

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

where they are going to go. So eventually we're going to be talking about worldwide collaborations in understanding drug effects in different populations, which is also very important I think. We have in the United States a very diverse population, and some of these effects vary by race, by ethnicity, by genetic background. And we can learn a lot about those factors by looking at different populations around the world and see what's happening.

Now, also we are -- we have implemented what we call Miniature Sentinel -- Mini Sentinel -- or the start-up for Sentinel. And Richard Platt is here to talk about that in more detail. But that will be testing, for example, how do you stand up a coordinating center that could do all these activities? And also be testing methods. How do you do a common data model? How do you query against that? And so forth for the type of analyses that we'd like to conduct.

Now, finally though, what's the broader context of drug safety and medical product safety which Sentinel is placed within? Well, for pharmaceuticals,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

in FDA we have done our Safety First Initiative, which is we are revamping how we look at post-market drug safety within the FDA. We're several years into that initiative, but we're trying to make sure that we bring the same project management, focus, and timeliness to our management of post-market drug safety issues as we do to the pre-market review process. And I think we are succeeding in that, although it is a gigantic effort.

Our Safe Use Initiative was announced several months ago. It has been very clear that regardless of how much we know about a drug, okay, it may not be safe unless it's used safely. And that means influencing the behavior of the health care system, as well as the behavior of patients to make sure that behavior is congruent with safe -- with the maximal safety and effectiveness of the product. And therefore, we can't simply go just to getting the knowledge. We have to actually make sure that we implement and follow the knowledge that has been gained, which is a greater challenge. And so our Safe Use Initiative is really about FDA collaborating with multiple partners out there

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to improve the safety of use of medicine so that the actual outcomes will be what we have intended. So knowledge is a necessary condition, but not a sufficient condition to ensure the best use of medicines for people and the best outcomes.

We also are revamping our pharmacovigilance systems at FDA. Dr. Hamburg referred to this as far as some new monies that we have. We're still in the process of doing that. We're currently running our Adverse Event Reporting System for drugs off a pilot that we built. I participated in that in the 1990s. And we hope someday soon to have a new pharmacovigilance computer system that will function better.

We're also working -- there were questions about that around the issue of medication errors. Both CDC and AHRQ have programs in this. The patient safety organizations that AHRQ runs and so forth, and we are collaborating with them. And that will become part of safe use in the future.

And we also are exploring the next electronic communications world that we're all in -- the social

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

networking and so forth. What a great opportunity to start getting information to people in a meaningful way, a way that they use every day to exchange information. It's just that we're going to have to figure out how to do that and we're going to have to get over a lot of things that we have a lot of dedication we have to completeness and in-depth information and everything. We have to utilize the new electronic communications in a way that meaningfully reach people.

So that's what we're thinking about at FDA. Now, what about the broader government efforts? There's going to be a huge push --there is on eHealth records -- and on making that a reality for the United States. What an opportunity, all right, for us with Sentinel and other similar efforts to, you know, improve the data sources. To do this correctly though we need standards. And FDA is working on, for example, the Rx Norm terminology. We're working with -- which is a drug terminology that can be used in these records that will be standard. We're also working on the Daily Med. The Daily Med is a repository of all current drug labels

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that's put up by the National Library of Medicine, fed by the FDA, that has the most up-to-date safety information in it, for example.

We also, of course, are working with those who are working on the health information interchanges of various kinds. These pipelines to move health information around will obviously help and empower the Sentinel Initiative with standards and so forth once they are more mature.

And then finally comparative effectiveness research. Somebody has already asked that question. How does what Sentinel is doing relate to what you would -- an effectiveness question you might ask. Well, these are actually just the flipside of each other. And I thought Jeff made a very good answer, depending on whether you're looking for increased seizures or decreased seizures, you know, that's a very small difference in your computer analysis. So we're working very closely with those -- AHRQ, in particular -- who is working on these methodologies because we see that they are very similar and actually may use some of the same

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

infrastructure at the end of the day, including data models and policies on data use and other challenges that we all have are shared in much of that research.

So in summary, Sentinel is a work in progress. Don't expect the Sentinel that we'll have at the end of this year to look like the Sentinel we have at the end of five years or 25 years. What is key is that we start building this capacity now and we relentlessly improve it as the technologies and the data availability and the science allows us to move in that direction.

There are multiple other work streams that are going to feed into this. The eHealth initiatives, the comparative effectiveness research -- these all will synergize as time goes on to allow us to have a much better handle on what is actually going on in health care and the impact of various activities and interventions on the health of our population.

So, I think we've made very significant progress in the last year for which I thank many of the people that I already acknowledged and many others and

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that the prospects for this moving forward are very bright over time, but it will require continued creativity, innovation, and dedication, and probably some money to get the job done.

Thank you. (Applause)

DR. McCLELLAN: Thank you, Janet.

Okay. Patrick.

MR. RYAN: As the slides are coming up I just want to thank Brookings and the FDA for the opportunity to present on behalf of the Observational Medical Outcomes Partnerships research team.

What I want to do today is just give you all a brief overview of OMOP and share with you some of the lessons we've learned so far through this effort.

So OMOP is a public-private partnership. It's managed by the Foundation for the National Institute of Health and chaired by the FDA, whose goal is to conduct methodological research to study and inform the appropriate use of observational data, both administrative claims and electronic health record data, for the goal of trying to identify and evaluate both

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

drug safety issues and potential benefits. This effort is really focused on conducting a series of research experiments to try to provide some understanding about how we could go about instantiating a network of observational data sources to use for these purposes.

Three of the primary objectives for that effort is to assess the appropriate technology and data that would be required for a network of data sources; to develop and test both the feasibility and empirically evaluate the performance of different types of analysis methods that could be applied across that network; and also to evaluate the required governance structure to figure out how we can as a public-private partnership work towards a common goal of better understanding the effects of medicines.

Part of the reason why OMOP was instantiated was because there was a clear recognition across multiple stakeholder groups that establishing the science of active surveillance is a hard problem. It encompasses a lot of outstanding research questions. And so what we sought to do was to establish a body of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

research that could at least begin to inform the process of questions around data, technology, methods, governance, and the intersection between all of those various components. So what we've established is a fairly ambitious effort to try to study and empirically evaluate how these various components come together and what could potentially become best practices for an active surveillance moving forward.

One of the most important points particularly related to governance is the need to establish and sustain a research community to be doing this type of work. Within OMOP's research community we really require and encourage and need active participation from all key stakeholder groups, including government, academia, industry, health care organizations, patient groups -- pretty much everybody in this room is being affected and is influencing the work that OMOP is doing.

From a governance perspective, OMOP has an executive board of 10 members that represent all of those key stakeholder groups. The board is chaired by Dr. Woodcock and also has active involvement from

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

everyone else, including Dr. Platt and Dr. Krall, who you'll be hearing from shortly. We also have two advisory boards also covering those key stakeholder groups, some of which you will be hearing from. And the project is being led by five researcher investigators. In addition to myself we also have Dr. Paul Stang and Dr. Judy Racoosin, who you'll be hearing from later, as well as Dr. Bram Hartzema and Dr. Marc Overhage. And finally, the project is being led by our executive director, Tom Scarnecchia, who is here.

We also have established a need to recognize a broad group of constituencies across developing methods. And OMOP has 17 methods collaborators. We wanted to test those methods across a broad array of data sources, and we've brought together a network of both six distributed partners and five central databases. And we're also trying to test technology in terms of both data access models and systems architectures. In total, the OMOP research community covers over 100 individuals that are participating in this effort to advance the science of drug safety.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

OMOP is a self-contained two-year research effort. We basically have completed the first year of this effort, and a lot of our work to date has been focused on studying the feasibility of methods. As we now transition into our third phase of activities, now it becomes kind of fun. We get to now test the methods against the data and try to understand what we can and cannot use these data for in the context of defining and evaluating drug safety issues. Once we learn that we hope to figure out how to integrate that into our ongoing decision-making processes.

One thing I wanted to highlight and keen off of Dr. Brown's talk earlier is the idea that there are multiple alternative data access models that are viable. One activity that we did was to conduct a survey to -- and honestly ask health care providers whether they'd be willing to participate in drug safety research and in what capacity. What we learned is there's multiple ways which we can accommodate establishing a network of 100 million lives. Whether it be a centralized model, a distributed model, or a federated model. And one of the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

things OMOP is focused on doing is trying to empirically evaluate and learn from two of these models.

Specifically, we're trying to evaluate both the advantages and disadvantages of both a centralized model and a distributed network. For both of these there are safeguards in place to protect patient privacy. In the case of a centralized network, what we're dealing with is de-identified patient data whose access is governed through data use agreements. So the folks that have access to that data are only conducting research for the purpose of drug safety research. Across our distributed network the patient level data resides securely at our distributed partners who only provide us de-identified summary aggregated information as Dr. Brown highlighted.

Just to show you the diversity of the types of data that are included in the OMOP data community, in the center you see our central lab where we've built our own systems architecture and have licensed five observational databases, four administrative claims databases from Thomson Reuters, and one electronic

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

health record database from GE Centricity. On the outside of that you can see our distributed network for which we have six partners and collaborators in our research. Those include the Reaganstreith Institute, Humana, Partners Health Care, I3 Drug Safety, SDI Health, and the Department for Veterans Affairs.

So as Jeff actually highlighted in his slide, one of the key challenges here is that every database is structured fundamentally differently. And we, too, are trying to evaluate the viability of using a common data model to organize the data in a common representation. OMOP has established a common data model. This model was developed with broad stakeholder input and expertise both from our advisory boards and from public input. This model was developed purposely to accommodate both administrative claims and electronic health record data. I'm happy to say that at this point we have successfully applied this common data model across our data community, so we know that it is both feasible and that we're learning about how this model could accommodate the types of research we're doing.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

The common data model -- the depiction of it here shows you that we really are focused only on the data elements required for active surveillance and not all observational data that might be available. But the common data model is publicly available as are all tools within OMOP. If you go out to our website at [omop.fnh.org](http://omop.fnh.org), you can download both the specifications, as well as the source code and other materials associated with this effort.

One specific item to highlight about our common data model is the use of standardized terminologies -- the need to be able to make sure that we're using the same languages across our disparate data sources. This actually became particularly apparent as we looked at our diversity of data sources and recognized that not everybody coded drugs and conditions the same way. This is particularly true with conditions as we think about the fact that Health and Human Services are going to require us to convert from IC9 to IC10 starting in 2013, which means we're going to have data in various different formats.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

The standardized terminology is one way to allow us to accommodate that. And we have established standardized terminologies for conditions in drugs and procedures, and this has also been something we've developed and is made publicly available. To Dr. Woods' point, we are using Rx Norm as a central tool to be able to accommodate drugs.

So once we have this common data model in place, now we have an opportunity to apply various analysis methods and provide structured analysis results back into our research community. Really the heart of the OMOP research effort is methodological research in developing methods. And one of the things that we've been quite struck by is the diversity of perspectives and approaches that the community has brought to bear on this problem. There have been interests in adapting disproportionality analysis methods, some of which Dr. Nelson highlighted early in her talk. And we found that there is actually a variety of ways that you could even apply a DPA method to these data.

We also have collaborators who are

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

implementing approaches for exposure-based techniques, such as cohort screening and high dimensional propensity scoring. We are actively exploring the use of sequential methods and have an ongoing collaboration with Harvard Pilgrim and Group Health to study how to implement and enhance the maximized sequential probability ratio test and the conditional sequential sampling procedure methods. But we also have collaborations going on with folks that are thinking about case-based approaches, such as case controlled surveillance, self-controlled case series. We also have methods about logistic progression for statistical relational learning. And if that weren't enough, we've also initiated the OMOP Cup, which is actually a methods competition whereby we are asking anybody else if they've got some bright ideas about how to tackle this problem, to come to bear. We've shared with them simulated observational data that we can then evaluate their methods. And so far we've actually learned quite a lot from some of the respondents who really are outside of the inner circle -- the folks that are in

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

this room that really brought some interesting ideas to bear on this problem. So we're pretty excited about that.

What we are doing with these methods is that we are implementing these programs as standardized procedures. And we're making all of these programs publicly available. Every program conforms to our common data model, so if you're a data provider and you were to convert your data into the common data model, you could take these programs and run them in your environment. The real goal here is to develop standardized procedures that could be applied and developed to analyze any drug in any condition. For the scope of OMOP, we're restricting our research to a specific set of drugs and conditions, but we are trying to develop these programs so they could be used more broadly for whatever purposes that any stakeholder may have. We really do believe that by making these publicly available that we can promote transparency in research and make sure that we all have a shared understanding of how to conduct this work.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So just to kind of summarize for you the overall effort that OMOP is conducting, we've now established a data community that represents the diversity of different data sources that are out there. We are starting -- we are building a methods library of which there are now eight or nine programs already available. Probably ones being posted as we speak. But the idea is to take any idea that anyone has about the appropriate way to analyze these data and to bring them into the fold so that we can empirically evaluate them. They're all being developed based on this foundation of using a common data model. And for OMOP's specific research, we are focused on studying a specific set of 10 products. These are mature drugs or drug classes for which we believe we have a solid understanding of the safety profile of these medicines. And we're studying the application of those methods across the data community for two specific analysis problems. The first is monitoring of health outcomes of interest -- the idea that you know the outcome you're interested in and you're interested in surveilling over time to see

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

whether you see a relationship. We've identified 10 health outcomes of interest, and we've gone through a -- as Vinnett said, a painful honor of going through the exercise of defining these health outcomes of interest and figuring how we can apply them across this OMOP data community.

We're also exploring the potential use of these methods for identification of nonspecified conditions. The more open-ended question of can we find relationships that we didn't previously hypothesize. For both of those research questions, we're trying to explore the relative utility of these methods against these data sources for their ability to identify relationships across an entire database, as well as how quickly they can identify those relationships as data accrue over time.

So the goal here is to try to determine what methods most reliably identify known relationships and can discern them from false-positive findings. Clearly this effort hopefully is going to answer some questions about what data and what methods could be applied in

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

this environment, but, frankly, I think the real objective here is to establish and engage a research community who can be working hard to think about what is the appropriate science that we can apply to active surveillance, such that when emerging questions come up we do have the ability to take the right tools and the best practices and the expertise and training we've now developed and use that fully for purposes of supporting the public health mission of the FDA.

So with that I'm going to stop. But I guess we'll take questions afterwards.

Thank you.

DR. McCLELLAN: Thank you, Patrick.

(Applause)

DR. PLATT: Well, it's a pleasure to be with you and to be part of this panel.

Like Patrick, I'm here on behalf of a very large number of people. If you think of the Verizon ads on TV in which a fairly mild mannered guy says, "That's okay. We're right behind you." And then the camera pans back and there's an army of people. There are, I

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

say, here over 100 collaborators. It's really close to 200 of us who have been working on these activities.

Now, I'm pleased to be able to tell you what's happening today, but really mostly what I'm going to be talking about is a promissory note because Mini Sentinel is just taxiing down the runway. We're in the process now of working with the FDA to determine what our Year 1 activities will be.

That said, let me take you to a slide of Dr. Woodcock's that she's graciously agreed to let me use that lays out our marching orders for the Mini Sentinel program. There are really two big pieces. One is develop the coordinating center and the second is to develop and evaluate methods in safety science. And it's not really fine print under that -- is the coordinating center has to have access to at least three different data environments; it has to convene a planning board; and it has to develop a means of secure communication. And then in the methods arena our requirements are to choose and, if necessary, develop methods for both epidemiologic and statistical analyses

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and to test them. So this is very much of a theme of the entire morning's discussion, and I'm happy to be able to take advantage of, A, the earlier presenters' comments, but also as Mini Sentinel, we intend to take advantage of all of this work.

Here are the organizations that are currently part of the Mini Sentinel. We beat at least three environments by quite a number. There are 28 organizations that are sort of formally contracted to participate. And those include organizations that are data holders and every organization -- some organizations that are bringing investigator talent and expertise, but every organization, including the data holder organizations, are bringing important investigator-level expertise to bear on this. The investigators are the heart of the Mini Sentinel activity, and include people who have been working on these topics in a variety of ways, both technically and conceptually. And so some examples include all of the Vaccine Safety Datalink site principal investigators are participating, and the principal investigators of 12 of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

AHRQ's Centers for Education and Research on Therapeutics, with the eyes of seven of the AHRQ decision centers. Those are developing evidence to improve decisions about effectiveness centers. Twelve of the investigators are now or ever have been members of an FDA advisory committee. There are three who are members of the IOM Future of Drug Safety Committee which in my view had a major impact on setting the FDA on the course that it is on now. Four presidents of the major professional organization for pharmacoepidemiologists and leadership of the C-PATH Institute and the data environments include -- altogether soaking wet include 60 million individuals for whom there is administrative and claims data for 10 million of those that are linked to electronic medical records. There are 88 inpatient facilities and a large number of device and disease registries.

The coordinating center org chart looks like this. The planning board includes representation from all of the organizations that I mentioned to you plus FDA. There's a Safety Science Committee; an operation

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

center, which is based in my home institution at Harvard Pilgrim and Harvard. Inside the operation center is a scientific operation center and a management operation center. And the Safety Science Committee oversees three corps data, methods, and protocol where the heart of the work is being done. People who are leading those activities are Jeff on the scientific operations; Kim Lane doing management operations; and myself. They have wisely not given me any real responsibility. Brian Strong and Wayne -- Pam and Wayne Ray at Vanderbilt co-lead the Safety Science Committee; Leslie Curtis at Duke; Mark Weiner, who is here from Penn; the data corps, Jennifer Nelson and Sebastian Schnaweiss at the Brigham Methods Corps; and Betsy Crushellis in Iowa; and Shawn Hennessey at Penn for the Protocol Corps.

The antecedent concurrent activities on which we're drawing are these. We've already talked about the Sentinel contractors' reports and the OMOP. It's important that each of the FDA centers is doing important work in these areas, and we intend to draw on that as well, as well as the CDC Vaccine Safety

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Datalink. The other couple of things that are providing a lot of information for us include the project called Prism, which is currently evaluating the H1N1 vaccine's safety and is teaching us a lot about how you put things together on a very large scale. And wrestle with some of these issues about public health practice versus research.

They recently completed meningococcal vaccine safety study that to my knowledge is the first of the studies that really worked at sort of national scale using very large health insurers as working as a -- in a coordinated way using common data model. And AHRQ's work in supporting foundational work in the development and use of distributed research networks has been extremely important to us.

There are a lot of challenges in addition to the things that have already been mentioned. Things that are going to be specific challenges that Mini Sentinel really sees as its major -- as its major work are the fact that it's going to be important to be able to evaluate many different kinds of exposures, many

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

different kinds of outcomes, and many different types of patients in a great variety of highly diverse data environments. Now, these antecedent studies all have one or more of those issues. I don't think any of them puts them altogether in quite this way. Additionally, there is the need for timeliness in both detection and follow up. We need to avoid false alarms, and we need to be able to do a fair number of things at the same time. Finally, there's going to be a need for surgery capacity because you just can't plan with this kind of work.

I think the two that are most important here are this -- what I see as often sort of needs that are intentioned with one another. One is timeliness, and the other is a form of accuracy. If we say we want to know at the very earliest moment that there is a problem, then almost by definition early on we won't be sure whether it's a real problem or not. And Dr. Hamburg started that discussion and several other speakers have addressed the fact that really developing a robust and well understood set of guideposts for how

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to do that work was going to be, I think, central to the work of Mini Sentinel because if we can't get that right then it's going to be very hard to make Sentinel be a real operational program that is a public health asset.

The other leading edge boomers in the audience will recognize this episode of "I Love Lucy" in which Lucy and Ethel were working on a conveyer belt. And they were -- it's the chocolate factory. And they did perfectly well until the conveyer belt sped up. And then all hell broke loose. And one of the things we're going to have to learn is what does it take to make an activity like Sentinel work at industrial strength, to work all the time in ways that are highly reliable.

I've had the privilege of being involved in most of those antecedent activities that were on that slide. And I'll say that every one of them has taught us a great deal. But one of the things we've learned is there isn't any organization yet that's capable of really making this work in a way that it doesn't have to sort of go back to the shop for repairs at fairly frequent intervals. And that's an important piece of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

what we're going to have to learn.

So having said all that, here are the key features that we're working on with -- that we're working on with FDA.

First of all, it's a contract. This is FDA's activity and we're the effector arm for FDA. And so although I showed you there's a planning board that has all of us groups participating along with FDA, FDA makes the decisions and calls the shots.

Secondly, it's our intention to look at all the products that FDA -- all the medical products that FDA regulates. Our expectation is that the first year is going to focus principally on drugs, but we're trying to build for the ability to look at everything.

Next, Jeff pointed out that there's lots of kinds of data, as has Patrick. Our intent is to look at all of these. Near real-time means current data, but the question is how current is that data? There's another kind of tradeoff that we're going to have to make, which is the more current data is the more it's likely to be incomplete and wrong in certain ways. And

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we have to understand when it's good enough for the purposes we want to be able to use it for.

I'll skip over this in the interest of time because it's another version of the comments that Jeff made about what you need and when you need it. We will focus initially on the above-the-line kinds of things -- things that are almost always necessary for most kinds of activities.

The coordinating -- part of what we want to do is learn what a coordinating center for Mini Sentinel would have to be able to do to make this activity work and work well for FDA. I've listed here half a dozen kinds of things that we think a coordinating center has to be able to do to make Mini Sentinel operate. Another thing that we learned in these antecedent studies is not only can you do one thing well if you focus on it, but doing one thing well takes a very long time to get going. The start-up time ranges anywhere from six months at a dead run to a couple of years. And that won't work for FDA either.

We expect to be using a distributed network

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

model for -- largely for the reasons that Jeff articulated. And we're going to have to be attentive to this idea of balancing the amount of local decision-making and control with ability to operate quickly. We expect to be -- to try to be thoughtful about how to implement the kinds of active prospective surveillance techniques that Jennifer outlined to both identify signals and confirm them.

Identifying signals is in some ways the easy part of the job. Confirming them is tough for a whole variety of reasons, not the least of which is there's an enormous sense of urgency to be able to distinguish the real signals from the false signals because the techniques we use generate signals that prove not to be of interest. The experience of the Vaccine Safety Datalink has been that -- the signal that Jennifer mentioned -- here's my version of her slide of the MMRV and seizure thing -- was one of about a dozen signals, I think, that the -- that have emerged. The other -- okay, it's 10. But the other signals have been ones that for one reason -- it's not a problem with the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

statistics or the statisticians, it's issues about -- it's a whole variety of issues. There are nine different reasons for nine different false-positives. And we have to be able to sort that out.

It's very clear that no matter what we plan to do, we have to be able to respond to ad hoc queries that come up because FDA needs to be able to answer questions that weren't on the agenda yesterday. And finally, we intend to put a fair amount of work into additional methods development, parts that OMOP may not be able to get to that will sort of complete the repertoire. We think there is additional work that we might be able to contribute on being -- on making a distributed network work both efficiently and in a way that maximizes the local data holders' control. And we clearly have to pay attention to understanding how different kinds of algorithms that use electronic data perform when you compare them to truth, usually as identified in medical records. And finally, we're going to have to pay quite a bit of attention to the privacy and public health practice versus research issues that

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Kristen identified.

So we're printing up wallet-size cards for all of our 200 investigators that have this information on them. We were really pleased when we were awarded this contract to find that this URL had been unclaimed. And so we reserved it. You won't find anything there yet, but we intend to be as communicative as we can about the progress we're making. And we invite you to take a look there.

Even though 200 is a lot of collaborators, we know that that doesn't include all of the really good talent in the nation. If you are or you know someone who would be interested in collaborating with us, please drop me a line. It may take me a little while to get back to you, but we'd like to engage as many individuals and organizations as possible.

Thank you. (Applause)

DR. McCLELLAN: Thank you. Thank you, Rich.

And to all of our panelists.

As people begin to make their way to the microphones for questions and comments, I'd like to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

start with one for Patrick. You sort of left me hanging about the Methods Cup that OMOP has to encourage innovation. And I understand that you've already made some initial awards to people for some innovative work. Can you talk just a little bit about who won and what they developed?

DR. PLATT: Sure.

So somehow the OMOP Cup is like the sexiest thing that our project is doing, apparently. Everybody likes a good competition. So the idea was that we provided simulated data out in the public community and asked anybody who was interested in basically providing prediction of what they thought were the known relationships and the data source. We had a progress prize announced in November, and the final grand prize will be announced in March 2010. Even with the progress prize, to date the current champion of the OMOP Cup actually had an innovative approach.

It was a data mining technique that was completely different than anything else we had tried. It was based on random for us. And as I talked to this

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

individual he was quite engaged in the problem, but hadn't been working in the health care space. He had been working on predictive modelings for getting spam out of your inbox. And yet to me it sounds like that's exactly the kind of individual we need to be able to bring into this research community to bring new ideas to bear and think about the problems. So, you know, he's the current leader on our interactive leader board, but anybody else in this room who has got good ideas, I encourage you to go out to the competition and try to unseat him as the leader.

DR. McCLELLAN: Thank you. Let's go down here.

MR. GREGERMAN: Milt Gregerman, Public Health Resources.

My question is for Dr. Woodcock, but others may comment, too.

First, Janet, I want to thank you very much for the excellent update on the FDA activities, which I'm sure will stimulate a lot of discussion throughout this day. And also for the federal acronyms test. That

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

was fun.

The question is basically, as I'm sure you know, the National Cancer Institute and the NIH is really C.A. Begg projects expanding considerably to go beyond cancer and also for international collaboration. And I'm just wondering about the extent -- and also they're learning health care system issues that I know have been of interest to you. And so I'm just -- I want to get some sense of to what extent and how is FDA working and collaborating with those folks to ensure that both of you can use each other's information effectively.

DR. WOODCOCK: We've been collaborating extensively with C.A. Begg. And in fact, we owe them a fair amount. They have helped us develop what's called our JANIS Data Model, which will be -- is the model we're using from clinical trial data. We plan to -- FDA has probably the largest repository of clinical trials in the world. I think that's probably undoubted. However, much of it is in paper, and much of it is in various electronic formats and inaccessible to analysis.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

This is mildly described as a tragedy. The JANIS Data knowledge will enable us to construct an analytical warehouse to put these data into both prospectively and retrospectively. And, you know, we're also collaborating with SEDISK on the formats. So, we are collaborating extensively with C.A. Begg. We know - - of course, they have multiple activities they're doing, but we are working closely with them in this effort.

MR. DAWAY: My name is Mike Daway. I'm just here as a private citizens.

One comment I would make is as you try to go to scale this up from mini to industrial length, is go talk to some of your cousins in other agencies. One that comes to mind is the IRS, who has been working with a similar customer base, you know, essentially everybody. And about the same level of detail. And they've been after it for about 10 years. I think there's a lot you can learn.

DR. McCLELLAN: Thank you. Yes?

DR. HAAS: Joanna Haas, Genzyme Corporation.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

A question to Patrick Ryan.

First of all, the work that the OMOP group has done is -- the productivity and transparency are really exemplary.

I did want to go back to an original decision with OMOP, which was very reasonable, and namely, to confine the attentions to drugs and to exclude biologic products and probably the other one, cellular tissues and so on -- gene products. And quite plausible for the goals that you set out.

And I just wondered, however, thinking about some of the implications in terms of definitions and the problems and the scope of the problems that those products have -- thinking about the increasing importance of those such products for the future and for the health -- the pharmaceutical dollar -- whether this represents a potential gap and how one might want to address it

MR. RYAN: So actually, it really does present an interesting challenge to think about how to analyze other products, such as biologics. One of the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

decisions we made for methodological purposes was we wanted to have mature products that we all could agree had well-established safety profiles. And most of the biologics are newer medicines for which we are still learning a lot about. And so there was concern about studying something that we don't actually know.

But one of the things we have actually explicitly done through all of our developments is we've been developing tools with a vision that they could be applied and used for other purposes. So, for example, in our common data model and the use of our standardized terminology, one of the things we explicitly did was we made sure we mapped not just prescription drugs as they might come in claims as NDC codes. We also made sure we mapped all of the associated procedure codes, which is actually the place where biologics commonly get recorded in administrative claims and electronic health record data.

And that way our data model -- we believe that it is scalable to the biologic -- to studying biologics and to studying the types of events that might

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

occur both in an inpatient or an outpatient setting. But clearly, there's a, you know, OMOP's really probably going to raise more questions than it's going to answer. So I think there's a huge opportunity to think about applying these methods and empirically evaluating them for biologics or other medical products.

DR. WOODCOCK: Many of the biologicals that are approved have NDC codes. So, you know, there's -- conceptually speaking, if you leave aside their structure, they're very similar to a drug. Okay?

Many of the other products that are regulated by the FDA centers are kind of out there. They aren't like that at all. And we do have problems, say, with devices. Like, how do you identify which device was put into someone? And where would you find that in a database? Or even how would you identify it? You'd have to look on the surgical record. Did they put down the lot number?

And so there are whole hierarchies of problems. Some of those relate to establishing terminologies for these things so they can go in the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

medical record -- in the eHealth records. So we're very aware of that and we're working with all the various centers and looking at all the various types of products to see how you would actually identify if a patient were exposed to one of them.

MR. SKOLER: Owen Skoler, FDA News.

My question is for you, Richard. I was wondering, you know, you mentioned that one of the biggest challenges is going to be ensuring the data is not analyzed too early in the process. And I was just wondering what's the danger of doing that? And what are you specifically trying to -- negative outcomes are you trying to avoid by ensuring that the data is not analyzed too early in the process?

DR. PLATT: Well, if you way make the data available as soon as you have it, there are two big risks. One is some of it is just wrong. And it is incomplete. And so you have to make decisions about is it correct enough or when do you have enough trust in it? And is the pattern of incompleteness one that might -- that might spuriously cause a signal to occur? For

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

instance, if you were to get access to certain kinds of information from some kinds of people sooner than we do from others, then you might get a distorted -- distorted result.

So that's actually an issue that's very much on our minds in this H1N1 vaccine Safety Study because the vaccine is being given during a period of a very few weeks. And so we've said to our partners who are providing the data, give us the data as soon as it comes in the door. Do it every week. And these are typically claims-level data. And it doesn't all show up with the same latency. So you can imagine ways in which the data might -- the data might arrive in ways that would increase the completeness for certain kinds of -- people have certain kinds of problems that might make the vaccine look as though it's more dangerous than it really is. Or for certain kinds of people.

So, it's -- and since we said give it to us right away there's been none of the usual kind of data quality checking that you would normally put things through. So those are the kinds of things that we're

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

trying to be wary about.

When we use these kinds of databases for standard epidemiologic studies or the kind that FDA has sponsored for quite a few years -- Janet mentioned those -- ordinarily, we let the data mature for months. Six months is sort of usually considered a minimum for saying the data are good enough to use. And when you say, no, let's have it after a week, you know, we're going to have to learn what you can trust.

DR. McCLELLAN: Thank you. Thanks.

MR. KOSNACK: My name is Arnold Kosnack. I'm an FDA patient representative.

It occurred to me that -- well, many of us have been concerned that in the context of standard clinical trials for drug approval there's a placebo effect that can mask the effects of drugs that are, in fact, efficacious. I'm wondering whether in the context of post-approval surveillance the same thing might be happening, particularly with the new blockbuster drugs that everybody is aware of as being, you know, the great new thing. And is this something that we need to be

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

concerned about?

DR. WOODCOCK: I think there are all sorts of sources of bias that we are going to need to be vigilant about. And just like in a clinical trial there's sort of overall biases that you -- the statisticians are probably nodding while I'm saying this, but, in fact, there's some regression to mean as you were saying -- and other things that may obscure certain effects. All right? In the -- out in the health care with the hype surrounding a drug or what we see in reporting is we see somebody reports something terrible happened to them with a drug, and especially now with these wonderful social media, all of a sudden everybody has that. I mean, when I was in medical school, every time we learned about something, half the class came down with it. So, you know, there are many pitfalls that we will have to face as we move forward with this. And I think we just need to continue to have transparency and continue to work on these methods and just do the best we can. Because what we're going to get is going to be better than what we have now.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. McCLELLAN: Yes. Back to the middle.

MR. KLINE: Tom Kline from the ACNP.

I would like a little more explanation of the common database in terms of the extremely wide variety of adverse events that might occur. And how do you get that into a common database?

And also whether there's been some attention paid to issues like anxiety, depression, which might also be side effects and hard to get them.

MR. RYAN: Actually, one very important distinction to make when we think about using observational data -- such as the administrative claims electronic health record -- is we're not actually finding adverse drug reactions in these databases. What we're finding is temporal relationships between exposures and the occurrence of outcomes. Oftentimes those outcomes might be the existence of diagnosis codes. And those diagnosis codes might represent either, you know, acute events or chronic -- you know, the existence of a chronic condition. We might also be using data such as the occurrence of procedures or laboratory results to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

try to infer the experience of the patient.

But one of the real challenges from a methodological standpoint and, you know, part of -- the fun part from the researcher in me is that what we are hoping to do is learn enough about the temporal relationship between exposure to a medicine and the effects that are observed in an observational database so that hopefully that information can contribute to some sort of a causal assessment when a safety reviewer actually has to say, "Does this drug cause an adverse drug reaction?" This information is not going to answer that question. It's just simply providing more evidence to either support or refute that assessment.

MR. KLEIN: I appreciate what you say. I'm just trying to understand in a common database how the various outcomes are dealt since there's such a number of things that you might find as an outcome.

MR. RYAN: So to be clear, our goal is to have a common data model that could accommodate all potential outcomes. And that means each data element that a particular database could have. So specifically,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that would represent all diagnoses codes and each one you could imagine could contribute to an outcome definition. And it includes all laboratory results that are available. So our real goal here is to try to figure out from that broad array of data -- how can we synthesize it to the specific things we want to look at.

DR. McCLELLAN: Thank you. Okay, two more.

DR. NIEDERMAN: Deborah Niederman, a neurologist and consultant, ex-FDA scientist, ex-NIH scientist.

I want to commend all of you on what's very impressive progress in this sorely needed area. Lots of methods development. Sounds great.

My question is perhaps anticipating next steps beyond presumably higher quality data and methods. What is going to be the process for assessing potential signals? What will be the criteria for identifying a signal? Saying this is a signal that arises above, beyond the noise and is "real?" And then what are the potential outcomes of that process?

DR. WOODCOCK: Well, I think it's fair to say

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

now -- to echo what Patrick said -- right now the FDA has to make decisions, as you know, all the time in the face of major uncertainty. And what we're seeking here is to have additional input into that decision-making process from a new source of information that hopefully will become both more robust and reliable over time. But at the moment it's FDA making these decisions based on information we receive from a side variety of sources -- post-market clinical trials, adverse event reporting systems, registries. And at some point these type of activities, although as you see they're just getting set up now. And so I don't think at this moment this activity will probably contribute a lot tomorrow to a decision that we would make. As Rich said, we do now -- we conduct under contract, pharmacoepi studies that then lead to conclusions or help us conclude about information that then lead to regulatory decisions.

So, it isn't like here we are today and then tomorrow we have Sentinel and it tells us what to do. Alright? It's that we have a lot of uncertainty. Now, we're seeking, by multiple activities, to reduce the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

amount of uncertainty about drug effects on outcomes, but at the same time we will have to continue to make decisions.

So, to answer your question I think what you should look for is a graded series of steps wherein information from Sentinel will start synergizing with our other sources of information as we make regulatory decision-makings. But right now the FDA is who makes those regulatory decisions.

DR. McCLELLAN: Okay. Last question before lunch.

MS. PONYLIGHT: -- and a comment. I'm Kathy Ponylight. I'm with the Drug Abuse Warning Network. I wanted to add one more acronym: SAMSA, Substance Abuse and Mental Health Services Administration. And we are part of the Federal Partners Initiative. We -- this survey -- and it hasn't been mentioned yet -- is a survey that collects data from about 250 emergency departments across the country on a daily basis. About 40 percent of the data are adverse reactions. And we also collect 450 medical examiner data on a daily basis.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

One of my questions is I haven't heard considered the impact of the increase in nonmedical use of pharmaceuticals and the combination of adverse reactions. So as that problem on the increase, how from a signal detection standpoint are you anticipating looking at that?

DR. WOODCOCK: The non-medical use? Is that what you asked?

So the question was how does the increase in -- the very unfortunate increase in nonmedical use of pharmaceuticals impact on this whole endeavor.

I think it's a very good question. I'm sorry I left SAMSA out. I'm intimately and sadly familiar with the DAWN data and the number of prescription -- the proportion of prescription medicines represented within that data base, it is a big problem. And the question really is if the exposure is not -- if I understand your underlying question -- if the exposure is not really well captured in the types of data we're looking at because that presumes that you had, you know, a medical exposure, then how will we conclude that?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

I'm going to turn that over to my partners on the panel here because I think that is a difficult question.

DR. PLATT: That's really the answer.

(Laughter)

In the limit, you may need to actually ask for information about exposures from individuals -- providers. Or ask the providers to ask the individuals about exposures that won't be captured in the systems that we're talking about.

That's part of the general -- that's at the very tail-end of how do you deal with signals. There's a whole variety of steps that you need to go through that range from the very simple, easy to do in an hour, to things that might take weeks or months to sort out.

DR. WOODCOCK: And my apologies for leaving out SAMSA in my acronym. I probably got tired or writing all the different letters, but it's a very important partner for FDA.

Thank you.

DR. McCLELLAN: Okay. Let's thank Janet,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Patrick, and Rich. (Applause)

We will look forward to an update on all these exciting activities at this time next year. And in the meantime, we're about to break for lunch.

Let me just point out that lunch is on your own. We'll begin again at 10 after 1:00. If you are not familiar with the area, in your packets there is a list of places to eat very nearby. And we'll start again at 1:10 sharp.

Thank you.

(Whereupon, a luncheon recess was taken.)

## A F T E R N O O N   S E S S I O N

DR. McCLELLAN: All right. Good afternoon, everyone. And welcome back. I hope you had a nice lunch and were able to stay warm.

Our afternoon session actually consists of three different panel discussions on a range of other issues in the implementation of active surveillance. And these are also going to be discussion-oriented. These are issues where there are a number of challenges and a number of ways of potentially addressing the challenges. And we all thought they would benefit from the kind of expert perspective and back and forth discussion that we wanted to make a hallmark of this process.

The first issue is ensuring patient privacy and addressing patient privacy concerns while meeting public health needs. As you know, this has already come up to some extent this morning. Then we're going to talk about the opportunities and challenges for developing Sentinel as a national resource for safety science, which could potentially go beyond FDA-specific

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

applications, as well. And the finally, an even broader question of whether it's possible to think about Sentinel as part of a broader multi-purpose network that uses health information for other evidence-development activities as well.

And so we're going to get right into Panel One. And they're up on stage with me. With us today are a group of legal experts to address the patient privacy and public health needs issues. This includes Verne Rinker, a health information specialist with the Office of Civil Rights at HHS. It includes Jeff Torres, partner with Lathrop and Gage, and vice president and general counsel of Qual Rx. Also, Deven McGraw, the director of the Health Privacy Project at the Center for Democracy and Technology. Kristen Rosati, who you heard from this morning, a partner with Coppersmith Schermer & Brockelman. And Kristen is not going to be making opening remarks since you already heard from her a bit, but will be participating in the discussion. And then Don Beers, the associate chief counsel for Drugs in the Food and Drug Division of the HHS Office of General

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Counsel.

Now, each of these panelists, except for Kristen, is going to take a few minutes with some opening remarks, and then we want to open this up to questions and comments from all of you and maybe from our panelists as well. The primary question for this panel is -- has to do with what approaches are available for protecting patient privacy, while also ensuring that the potential public health benefits of Sentinel are fully realized. This requires touching on a range of different areas of expertise and policy, including federal and state privacy laws, which Kristen talked about this morning, and Verne and Jeff are going to say more about now. It also requires an understanding of the data needs for safety surveillance and capabilities of modern health IT, privacy and security systems, and protecting those needs. And based on what we discussed earlier today, it seems like initially there are a number of surveillance questions, post-market safety questions that can be addressed without much, if any, transfer of personal level data across firewalls. So

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

perhaps we can explore that a bit further.

One near term question then is what are the necessary protections for data privacy in compliance with federal and state laws in the near term, and then thinking longer term, as Sentinel becomes more sophisticated, as Kristen was laying out this morning, there may be additional benefits in examining, exchanging patient-level clinical information or linking more sophisticated clinical databases at the patient level, so what further challenges are involved there.

And I understand, Don, that you're going to kick things off for us.

MR. BEERS: I asked to have a couple minutes at the start to sort of lay the groundwork, since I'm the one up here who doesn't really have any knowledge in this area. I'm the client, so to speak, working with FDA.

We -- as we envision Sentinel, we see this really kind of as three components, and we recognize there are more than that, but over here, we see the data holders, the people that have the PHI, Private Health Information. Over here we have initially the FDA, the people who have the questions they want answered.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Ultimately, there will be, as Sentinel develops, it will be more people over here. It will be not just FDA. It may be other people that have queries, and, in between, there will be a Coordinating Center; and in mini-Sentinel the Harvard Pilgrim Group is acting as a coordinating center. Eventually, there will be a coordinating center set up for all of the efforts of Sentinel.

Now, as we look at privacy information, well, we're saying okay, this is relatively easy. The people in the data holder segment here, they will have to have permission to use that private information, but they're not going to disclose it. They're not going to disclose it to the Coordinating Center. The Coordinating Center is not going to disclose it to the FDA.

Instead, they're just going to provide summary results of queries that are provided to them. And so we said, well, that's pretty easy. We've solved the problem in the short term, and we can talk about what happens in the long-term.

But then, as we talked with our colleagues, it appears there's some issues that we're going to have to deal with even sooner that we had hoped to.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And I was given for things that we should think about, and I'd like to ask the panel to talk about a little bit as well.

Suppose the query result produces what's referred to as a small cell. Suppose there are -- Dr. Platt will tell me if I'm getting this wrong. Just stand up and wave your arm.

Suppose there are only five people in a cell or only 10, is that PHI? Is that -- do you now have to worry about that being transferred even to the Coordinating Center in summary results? That's a question.

Suppose you look over here in this group here, the data holders, and you have a query that results in a need to get a little more information about the patient. The Coordinating Center says, well, we need to track this down a little bit further, and the data holder is -- it's a health plan. It's an insurance plan.

Well, they don't have that information, so they then turn and go back to, say, the hospital that has the record. Now you have potentially a transfer of PHI from the hospital to the health plan. It's all back on this

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

side of the equation, but you have potentially a use and a disclosure one needs to deal with.

Another example in some multivariate analyses -- and someone else will have to explain multivariate analyses to you, if you don't know it, and you probably all do -- there are situations that arise in which you need to know at least the month and year of administration of the product, and that is PHI under conventional definitions.

So that's something that we potentially have to worry about. And, then, the fourth thing that was raised has already been previewed a little bit what about situations where you want to link data from different databases. You know certain information from one database, but you'd like to know -- and it was mentioned this morning -- you know, how does this link up with, say, a death database or cancer database or some other database.

How do you deal with those issues? So I've asked the questions, and now I'm going to sit down and other people give the answers.

DR. McCLELLAN: Very good questions. Verne, do you want to start off with some answers or do you have more

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

questions, too?

MR. RINKER: Well, it wants to do it from here?

DR. McCLELLAN: Yeah. That's fine.

MR. RINKER: I'd probably prefer to have more questions, but my boss doesn't like to give answers, and I have kind of taken to that.

Thank you, Don and Dr. McClellan. I thank the Brookings Institution and FDA for pulling this together. It's great for us to be involved in this type of an activity for the development of such an important public health tool such as Sentinel that's coming onboard.

I'm happy to share the stage with a few colleagues that are not unfamiliar to OCR and to see such a large attendance in the group, particularly interested in the privacy section and interest.

As the Department and healthcare community look to the promise of benefits and improvements achieved through the electronic health records and the power that that represents, OCR is happy to support the new promising public health initiatives that are aimed at ultimately

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

improving care for patients.

Moreover, it's good to see that privacy continues to be an important element when looking towards the promise for future technologies. While the technology and the data may grow richer, the ultimate need to continue to find that right balance, the right balance of privacy, remains.

And it's good to see the efforts continue -- and it's demonstrated here -- to keep an eye on those privacy interests and that ball as it moves.

With particular regard to Sentinel, it's been great to see that efforts on the part of the FDA and their staff and others to consider the privacy implications not just in its current incarnation, but also looking down the road to where Sentinel may grow. It's good to look at that now so that it doesn't become a pitfall later.

I'm not going to go into a lot of detail about the privacy rule. Kristen did a great job earlier today about that, and has a very comprehensive analysis and report. Again, kudos to the FDA for looking ahead towards that as an activity, as an issue.

It is true that OCR has gained a bit of weight as

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of late. If you're familiar with Aura and high-tech, we will be expanding whom we reach out to and look at on occasion, and we will be expanding with potentially much larger CMPs when there are violations.

Regs are due on that, but that is certainly something to keep in mind as Sentinel evolves, because the big sea change there is that business associates are going to be liable in some form or fashion going forward.

You're going to hear a couple of terms, and you've heard them -- some already -- de-identification, limited data set or LDS, for short, minimum necessary. That theme is probably key: The less data, the less of a concern.

And that's something again to watch out for the future. You hear already the writing on the wall that says we may need to link data sets together. We may need PHI. It's enough for de-identified now for maybe low hanging fruit, but as it continues, it's important to have these discussions now so that you know where you're going and can build in those important privacy protections.

One of the maybe good news things is that once

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

it's de-identified and it leaves the covered entities, then it's no longer subject to the Privacy Rule. That doesn't mean that it's not subject to a host of other privacy laws that are out there and regulations, either on a state level or ethical or fiduciary obligations as well. It's still data. It's still important to protect that.

The second is that even as there's a need for greater identifiable information, it doesn't necessarily mean that HIPAA, for example, stands as a stop to that. It doesn't mean that it can't -- information can't flow.

The Public Health Disclosure is pretty widely recognized, and even beyond public health, you get into research disclosures, the limited dataset. So there -- I like to think of HIPAA and the Privacy Rule as being where there's a will, there's a way. It's written in a manner that recognizes a broad range of activities. And Sentinel is one incarnation of the age-old attempt to find the balance between recognizing individual data and making use of that, ultimately in the effort to try to help improve the patient's care.

So, again, I won't talk about privacy specifically with the HIPAA Privacy Rule. We'll leave that

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

for questions and concerns, but again, thank you all for your attendance and the focus on privacy particularly.

DR. McCLELLAN: Great, Verne. Thank you.

(Applause)

MR. TORRES: While I'm waiting for the PowerPoint, I'll introduce myself. I'm Jeff Torres. I'm a partner at Lathrop and Gage in Chicago. I'm also VICE PRESIDENT AND GENERAL COUNSEL for a government contractor that received a contract from the FDA to take a look at 50 sets of laws around the country that potentially could impact the Sentinel Initiative, Qual-Rx, Inc., and its legal affiliate QRX Legal Solution. You can go to the next slide.

A service-disabled veteran-owned business. My colleagues and clients are in the audience -- Mark Ginter, Margie Clay, and a partner of ours, Chuck Bell at BPSI.

The problem for database holders, as we see it, is there's a dual system of liability in the country, and Kristen and I had a really good discussion at lunch, and I'm not a healthcare lawyer. I'm a financial services litigator, and I've been doing that -- this for about 15

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

years.

And in a lot of respects, the financial services world is ahead of the healthcare world in terms of data security and standards. There are three sorts of -- or three bases -- of liability, which I think are more stringent than HIPAAA, which was the tasks that QRX Legal Solutions was tasked with, one being tort liability.

Those are the common law torts that have evolved over time -- the other being statutory liability. There are a lot of state statues that prevent the release of confidential health information, primarily starting in California in 2005, when ChoicePoint inadvertently released 163,000 financial records and incurred a \$50 million fine from the FTC and over \$30 million in other costs.

I think it's important to always go through the HIPAA Preemption Analysis. The HIPAA Privacy Rule preempts state law unless one of the following four occurs: There's a specific determination made by the HHS Secretary; state law either relates to the privacy and individually identifiable health information and these more stringent.

So, again, the focus of the QRX Project was to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

look at regulations, which were more stringent than HIPAA because they do not preempt HIPAA.

The third state law authorizes public health reporting, and that's always the case or state law requires health plans to report or provide access to certain information.

Again, the dilemma: What databases are subject to state law? It was helpful to hear today some of the participants and stakeholders talk about the various databases that are going to be included in a mini-Sentinel, but as the project evolves over time, it's important to keep these sources of data clear in order to keep liability concerns limited.

Again, it's difficult to determine whether state privacy laws in many cases are more stringent than HIPAA. There is a \$51,000 study out there, which I have not seen, but the Health Insurance Association of America has published a HIPAA Preemption Analysis. The study itself cost \$1 million, and for \$51,000 a crack, you can take a look at it.

We attempted to do the same thing, but there have

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

been numerous studies -- and this is a gray area, to some extent in the law. And again, my background is in financial services and talking to Kristen it appears as if the financial services world is a little ahead of the healthcare world in terms of understanding the scope of liability and data security.

Some inconsistent sources of state law -- and, again, you're looking at more stringent data security or requirements to keep data confidential. These are just some in which health records are maintained -- criminal procedure, state departments of aging. And you can just read the list.

Incidentally, the PowerPoints are going to be available on the website, so you can take a look at these, and, if you have questions, you know, call any one of us, but, as I'll get to in a minute, we attempted through QRX and Lathrop and Gage to take a look at all 50 sets of state laws, and our report will also be published within a few weeks.

We also have come up with a Critical Action Matrix. It's an Excel spreadsheet, which goes through the HIPAA Preemption Analysis. We actually took a look at the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

State of Kansas in depth. Over 200 state law privacy fields, if you recall the slide previous, looking at all the different types of data held by all the different state agencies.

We came up with 200 separate fields of data, 20 of which were gray areas, we concluded, within the HIPAA Privacy Rule. And this is in Kansas, again -- genetic information, donor databases, medical records resulting from arrest. That's a gray area. Data stored without court orders in some cases and data stored without specific state permission.

Just some other odd gray areas around the country and there are hundreds of examples, and, as I was telling this -- as I was mentioning to Kristen, any crafty plaintiff's lawyer -- and I've been on the defense side for a lot of years -- but any crafty plaintiff's lawyer can come up with, you know, any type of hypothetical really, but there are specific state statutes out there which have more stringent requirements than HIPAA, one of which I'll draw your attention to is Idaho individual pharmaceutical records.

You actually need specific permission from the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Department of Health and Human Welfare to disclose any individual pharmaceutical records without state permission.

As we discussed also at lunch, there are types of -- types -- state regulations related to controlled substances, birth defect studies.

In Wyoming, any medical records directly or indirectly identifying patients you need specific permission to disclose as well.

Again, the universe is huge. I encourage you to take a look at this Critical Action Matrix we put together, and there's a HIPAA Preemption tab with 200 data fields for the State of Kansas alone. And every state should have its own similar analysis done.

Practical pointers very quickly: Know where your data is held and where it's disclosed. Your liability is different depending -- or it could be different depending on where data is held or disclosed. Secure proactive consents from government agencies, if government agencies have the ability to give that proactive consent. Again, take a look at the Critical Action Matrix from Kansas, and also know your breach notification obligations.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Again, referring back to ChoicePoint, starting in 2005 and subsequent to 2005, 45 states have breach notification rules, many of which are different depending on the risk of harm, who has to be notified, when the notifications need to take place, and the like.

And, of course, there's always data breach insurance. Thank you. (Applause)

DR. McCLELLAN: Thank you. Deven?

MS. McGRAW: Thank you very much for the opportunity to be here. I also want to start by telling you a little bit about who I am and whom I work for and who I represent, which is -I don't have clients. I guess I'm one of the few lawyers at the table who doesn't have any clients.

I'm with the Center for Democracy and Technology, which is a non-profit 501(c)(3) public education and advocacy organization that is primarily based here in D.C., but we just opened up a small office in San Francisco about a year ago, so we're trying to conquer California. Why we chose to bite off that nugget of all 50 states, I'm not so sure, because it's quite complicated out there.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

But, nevertheless, we are -- I guess if we represent anyone's views, we try to represent the view of the consumer, the patient, the public in this space, and here, you know, obviously the privacy considerations come right to the forefront.

But it's not the only reason why patients and consumers are interested in what's going on with Sentinel.

People also care about making this data -- having this data more accessible to get them better care and to improve our public health surveillance.

So, in some respects, we have kind of a dual challenge, and that is to make this happen, at least with respect to making sure that the public agencies can fulfill their missions to keep us safe.

On the other hand, we can't do so in a way that so careless that, in fact, we're not -- we're flippant with the way that we use data, and we end up with the ChoicePoint example in healthcare, which, by the way, we can engineer these things as well as we want. We still we have humans operating the computers, and so things will inevitably happen.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

But if we're not careful to structure this in the right way and we're not careful about who gets access to this resource we're creating and for what purposes, one really bad example is going to blow up the whole thing.

And that would be quite unfortunate, again, because the public, again, has dual interests here: the privacy piece and making the data available to get this done.

And one doesn't and shouldn't necessarily be the obstacle to the other. In fact, privacy rears its head in really two ways; one as if you don't address it, you're in big trouble. The second is it becomes sometimes the excuse for not moving forward.

Either one would be very unfortunate in this regard. So I'm glad to see that we have people on board addressing these things in a very careful. The devil is always in the details, but I think there is actually a way forward.

I think Kristen's presentation -- I was sorry that I missed it, but I read her paper -- made clear that it's not an issue of can we or can't we, but how, because I

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

think we all understand that this is -- that we need to do this.

I think the other thing I'll say is that another thing that I do is to serve on the Health IT Policy Committee, which is the Federal Advisory Board to the Office of the National Coordinator for Health IT. And I was recently appointed to co-chair its Privacy and Security Work Group.

And many of the issues that we are facing in standing up the Sentinel system and thinking about ways to expand its use for public good going forward arise in other contexts as well and are ones that we're grappling with.

So I would hope that we would continue to kind of cross pollinate our knowledge and our discussions so we come up with a sort of consistent set of policies for how databases get linked, for example, and circumstances under which one is permitted to do that.

So on some of Don's questions, I'll say a couple of things.

I think that there are two -- two -- there are probably more -- but two critical questions come probably

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

most immediately to mind: Who's getting access to the data? What data are they going to access to? Okay. So there's three. And for what purposes are they permitted to access this data?

We're establishing this, at least initially, as a federated model; right? The data is staying with the original data holder, and we're not asking for entities to push data into a separate entity, at least not at this juncture. When we start to have those discussions, of course, that raises a different set of questions that we need to pay attention to.

And we're talking about data, number one, going to public authorities who are accountable to the public in multiple ways, and the data they're getting is not identifiable to most people. It's being presented in aggregate form. The FDA asks the questions. They get back the answers.

In my view, again, you know, I think there is law that's already on the books that permits this, and I think that that's just fine, because this is, in fact, part of what the public expects to be done with public dollars being spent to create this infrastructure for data

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

exchange.

It gets a little tricky when you start to push on those margins and think about things like well, we want more than the FDA to be able to access this data. Well, who and who decides? What sort of publicly accountable process will be in place to determine who and under what circumstances this data is going to get use, and how is accountability going to be assured down the chain?

The small cell problem that Don mentioned so that may or may not be PHI, I think, depending on what type of data you're talking about, but when you know that you have a small cell problem where the data may not look identifiable to the naked eye, but it wouldn't be too hard for a healthcare entity or the entity who might be receiving the data to put two and two together and link them up; it doesn't necessarily -- I mean the answer to that question shouldn't be well, then they shouldn't get the data, but there are ways and there are -- to hold people accountable for how they get that data and whether or not they re-identify it.

So, for example, if it's considered to be a limited data set at a data use agreement is required that

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

data use agreement should be pretty strict about here's how you can use the data, and, by the way, if you re-identify it and you start using it for some other purpose, you're in violation and we can hold you accountable for that.

I mean that's -- it's very important. I can't stress the accountability piece. And, by the way, that actually, in my view, applies with de-identified data, too, especially where we have considered it to be de-identified because it meets what's now called the safe harbor, where if you strip out certain data elements from a data set, it's per se de-identified and so, therefore, it slips out of the protection of the Privacy Rule.

And I think we know from some research that, in fact, that's not always the case depending on who gets the data and the data that they have access to that can be used to link things up.

And so I am completely in agreement with Verne that the less data, the greener you are with data, the less data that you've got in the set, the better off you are from a privacy standpoint.

But that should not absolve us of our obligations

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to make sure that the data is being used for the purpose for which it was given and that there's some way to hold people accountable if they're using data in ways that they're not supposed to.

It's really -- it's almost as though the downstream -- you know, you're allowing people to hold data and use it for a certain purpose. That should not turn itself into because we haven't crossed the "I's" and dotted the "T's" some blanket perm -- that suddenly becomes my data, and I can then use it for some other purpose.

If we're careful about how we structure this and hold people accountable to using the data in ways that they've committed to and why they asked for in the first place and that we think is legally authorized, then let's do that. Let's take care of it that way, and we will certainly go a long way to closing up some of the potential I don't want to call them loopholes, but pitfalls that could really trip us up in structuring this in a way that really does advance the public good.

DR. McCLELLAN: Deven, thanks very much.

(Applause)

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. McCLELLAN: All right. You deserve the applause.

Kristen, I know you weren't going to make any remarks, but any quick comments on what you've heard?

MS. ROSATI: I think that Deven's approach to this issue is exactly right on. We can talk all day about technical legal compliance, and there's -- where there's a will, there's a way. HIPAA is a fairly flexible law that permits us to do this. Some state medical record confidentiality laws are more restrictive and will, in fact, be a barrier to some aspects of the Sentinel if it's rolled out across the country.

But I think what we really have to focus on here to meet the public good of making sure the Sentinel Initiative happens but still respecting individuals' rights to privacy is to have transparency in the system, public involvement in creation of it, and accountability.

I think you were right on in focusing on accountability.

DR. McCLELLAN: Don, have your questions been answered?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

MR. BEERS: Well, there's sort of an attempt at the first one. I really thank you, Deven. You know, I think ultimately the question that people have had is is there something about the privacy challenge that is going to derail what everyone here, I think, thinks is a very good idea, which is the Sentinel Program.

And the consensus seems to be no, but it's going to be difficult, and we are still working our way through some of these issues. I mean if anyone in the room thinks we can't do Sentinel, then we should talk about that. But I'm content that we're going to work it out.

DR. McCLELLAN: Well, I would like to hear from more people in the room whether or not you think Sentinel can actually be done. So, this would be a --

MS. McGRAW: Can I ask a question? When you say can Sentinel be done, are we talking about phase 1 of Sentinel or Sentinel it is sort of dream of the future later phases?

DR. McCLELLAN: A good question, but while we're getting an answer to that, if you all do have some questions or comments, please make your way to the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

microphone.

There were some distinctions that many of you made between phase one, which in a simplified version is basically the summarized data rather than individual-level data, and phase two, which would involve more individualized data, but, as Don pointed out, I can see some benefits for him having a phase one that's got at least some limited use or limited trace back capability of individual-level data, so, Deven, does that change your answer to the question?

MS. MCGRAW: In some ways, the devil's in the details. So, you know, so some limited ability to trace back. You know, do -- are you going to tell me that I have a medical device in my body that's got a problem with it. Yeah, you know, I think I'm okay with that. And that information should ideally be conveyed to me by my healthcare provider and not someone whom I didn't expect to have the data.

DR. MCCLELLAN: Good. Now do you want to start?

MS. SILVERMAN: Yeah. Shelby Silverman, FDA, Office of Blood, which presents a fairly -- oh, along with

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the Office of Cell and Tissue and Gene Therapy, has some unique issues with regard to privacy, because now you're involving not just the patient who may have an infectious disease transmission, but potentially a donor who may need to know that he or she has a transmissible infection.

With de-identified data, I don't know how you would ever trace that back or solve that problem, and I'm interested to hear thoughts from the panelists on that problem.

MS. ROSATI: If I may? One of the ways that the industry handles that in the clinical research context, of course, is to have the data holder, who originated the data, be able to link that data with -- with individual identifiers or not sent to the recipient of the research data.

Then if the recipient of the research data determines that there is some adverse issue that needs to be communicated to the original person in the clinical trial, they tell the healthcare provider who conducted the clinical trial and they can link it up with the individual. So that would be possible.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

MS. SILVERMAN: You have a couple of issues here, though. You have a hospital that administers a unit of blood and you have a collection center that has the information on the donor.

MS. ROSATI: Mm-hmm. Right.

MS. SILVERMAN: And the communication between them may be difficult.

MS. MCGRAW: The challenge to link them. But I tend to agree with Kristen. If the donor gets that information from someone that they didn't expect -- reasonably expect would have access to their data, there's -- the fur's going to fly, if this is going to be a problem.

Where patients get up -- they don't necessarily -- I mean with some people obviously, you know, there are some folks for whom you can't possibly do enough on privacy. But the majority of people want their physicians, for example to have access to their data to use the treatment and then if they get information that's relevant to their health, they want it to be used to communicate with them.

It's a different story when that communication is occurring by an entity that they never knew even had the data in the first place.

DR. McCLELLAN: Through the physician is important. Next question?

MR. HARE: Jonathan Hare. I'm with Resilient Network Systems. One of -- I think it's worth noting there's a tension, actually a conflict between the mission of the FDA Sentinel Initiative and traditional approaches to privacy; so, for example, if you take de-identification that deals with sort of liability issues for people who hold the data, you lose the ability to create a sort of a longitudinal record from all sources about the patient. So you're losing most of the signal to figure out where the risks are.

If you de-identify it, you can no longer notify the patient or their clinician that this particular patient has risk factors right now, and you should change your behavior.

Going into phase two, I understand there's like multiple phases in Sentinel. And if you look at the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

original Sentinel sort of charter, it had -- it would get all sources of data for many different uses connected together and do decision support at the point of care in real-time to the clinicians and the patients.

And I think it's really important to set up a process where we work out what are the actual requirements to support that, not constrained by what's traditionally done or what the law says when talking about institutions using traditional methods to enforce privacy; but what do we actually need to be able to do, and what do patients actually want in terms of privacy in their dream world. If you can articulate those requirements fairly clearly, then people can innovate and try and solve them.

If you don't, what I always see -- and I'm sitting on so many committees and working groups and so on -- you always end up in privacy a bunch of lawyers and a bunch of technologists, and they start making these brutal compromises with the reality. And everybody hates the results, and data doesn't flow.

So if you have any thoughts about getting beyond that into a more aspirational mode in the future?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

MR. TORRES: I actually want to take a stab at that. There's no doubt we live in a federal system in this country, and we have 50 states and 50 sets of laws and regulations, and my answer is there's no excuse -- or there's no alternative other than the slog of looking at individual state regulations or laws that govern a particular database -- where the data is held or where the breach would occur.

There's just no way around that right now unless there's broad preemption by either HIPAA or by the Secretary.

MR. RINKER: I would actually -- I've looked -- there's been many 50-state surveys done. The Healthcare Leadership Council spent \$4 million on one back in 2003, I think, when HIPAA came out. And so --

MR. TORRES: I had no part of that one.

MR. RINKER: What's that?

MR. TORRES: I didn't have a part of that one.

MR. RINKER: Yeah. No, I've heard of at least 10. And it's good work. It's a good foundation, but what

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

it says is we need to find a fundamentally different approach.

One of the most healthy things I saw very recently was out of the ONC and the Secretary announced the interim final rule for certification for EHRs for purposes of meaningful use. And it was a -- almost tears of joy to my eye, because they acknowledged there are holes. There are certain areas where the standards aren't mature. We don't know what we're doing, so we're not going to designate a standard; right? We're going to open it up to innovation, and we're not going to insert something in here -- get the -- you know, go back and solve this problem.

And I think we could do something similar in this area. You know, it would just be -- this is what we aspire to. This is what we must do fulfill this mission; get a group together of all the stakeholders and then -- we found ways around those particular problems you solved. Those are solvable problems; right?

So how do we get that group together and actually solve it in the very near term, not wait -- I don't think this needs to be 20 years. I certainly hope it's not, because we're going to break the entire budget unless we

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

can solve problems about how do you move data, how do you inform decision-making and eliminate the conflicts between privacy and sharing of information, we're kind of doomed.

DR. McCLELLAN: Can I just make one comment. I thought -- I took your question initially a little bit differently than this idea of a group to solve the problem, but rather about focusing in on the areas where Sentinel sooner rather than later might benefit from moving beyond non-identifiable data and triggering these state issues.

And we've already talked about -- at a little bit of length one of those particular applications which is where you trace back the medical records, get confirming information for a case, but then also -- would also be in a position of informing a patient about some patient-specific information.

Don mentioned a few others: You know, what if a cell size is only five or three or something like that, but it seemed like there are potentially an identifiable -- I thought this is where you were going -- there are identifiable set of ways in which identifiable -- potentially identifiable information might be used sooner rather than later as Sentinel and we needed a way to handle

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

those explicitly to get back to Deven's point about, you know, what are you doing and how and who's getting the data.

Is that -- so I didn't mean to interrupt the thought of Kristen, but --

MS. ROSATI: Oh, that's fine.

DR. McCLELLAN: -- if you all could comment on that, too, I'd appreciate it.

MS. ROSATI: I think the thought that you're making, too, that there is this natural tension between privacy and the public good in some instances in terms of what we're trying to create here is a really good one. And maybe one of the things we all need to do is think about what the next steps should be in terms of protecting patients and the public if their information is used or disclosed in this process.

Like we perhaps need better laws involving authentication of individuals to apply for credit, so we all don't need to worry about putting a fraud alert on our credit reporting accounts in order to, you know, protect ourselves against identity theft.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And there's lots of other examples of how we -- expansion of the Genetic Information Non-Discrimination Act to life insurers and disability insurers.

I mean there's a lot of different examples of how we could do a much better job at protecting individuals if information about them is released, which it might be in a variety of activities that we're thinking about pursuing for the public good, including the National Health Information Network, the Sentinel Initiative, and other activities.

MS. MCGRAW: I think there are also a couple of opportunities to explore -- now whether the government will take these opportunities up or not I don't know -- but I think there -- I think the stimulus legislation gave us a couple of opportunities to explore this traditional dichotomy of personal health information that's identifiable; the one in the middle, the limited data set, which still has very specific criteria that we have to meet in order to qualify for it; and then de-identify data on this range, where, for any particular research query, there's some data that's needed and some that's not; and it doesn't necessarily fit into a neat little box.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And the privacy protections ought to either be expanded or, you know, the sort of mechanisms by which people have to go through and what data they can get access to it ought to be more restrictive the more fully identifiable it is; less restrictive the less identifiable it is -- a more sort of of a sliding scale and the HHS is required under ERA to do guidance on the limited dataset that, you know, I personally would like to push them to do more than just give guidance on how to comply with it as it exists today.

But instead to sort of think more about ways to make data available for these purposes that's lesser identified, because it's not anonymous, but still can be used. And that data use agreement is the most valuable tool of accountability that we have. It makes it much more appealing to me quite frankly than de-identified data, which just falls off the radar screen and is it really that useful.

DR. McCLELLAN: So developing this continuum is something that could fit into the HHS mandate under recent legislation. Who would H -- how would this be done? What's the right way to do it?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

SPEAKER: Someone has to write a regulation.

DR. McCLELLAN: Verne, you volunteer for that one?

MR. RINKER: We are writing plenty of regulations at this point in time. We are writing so many regulations.

Yeah, I -- it simply is one of the facets and (inaudible) and High Tech really did push this for us as well is to play somewhat of a larger educational role, and, although we do that currently, it is always something that we can seek to improve upon. We have been very busy over the past couple of years dealing with enforcement and enforcement has taken a front seat certainly in High Tech with increased penalty amounts and efforts at expanding who was responsible.

At the same time, that doesn't mean that everything else falls off of the OCR radar screen. Fortunately, as this gathering shows, there are many, many, many people involved, and HIPAA is only one small component of that.

It is a valuable component and one that is probably the starting touchstone for most entities. At the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

same time, it's not the end-all and be-all, and we've been fortunate to have relationships, for example, under the Patient Safety Initiative with ARC and certainly hopefully growing out of Sentinel to continue to recognize where HIPAA may need a little bit of buff and polish or where it can -- where we as OCR can do a better job at fulfilling the needs and listening to the consumers and the patients about where their privacy interests are best landed.

So round about saying that yes, we are here, and it's certainly good to be involved in these discussions and take that back. We are continually open for business and welcome comments and suggestions at any and all times, Deven, Kristen.

SPEAKER: (Off mike.) (Inaudible.)

MR. RINKER: And certainly to the extent that this can open up an exploration that we -- in -- to the extent that we are an enforcement entity, though, it does mean that we are somewhat limited than traditional entities such as NIH or CDC or FDA. We do not come with probably first and foremost the scientific expertise and experience that is most needed to guide those efforts.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So it's important for us to have those committees, such as Deven mentioned -- the (inaudible) Policy Committee, et cetera. And I think it's efforts like that that start the ball rolling to start both getting guidance out as well as looking at where -- where can something like Sentinel best be set up and what road blocks there are that the Department can actually do to ease and ultimately served that public health role that it needs to.

SPEAKER: I should point out, by the way, there are techniques, for example, to make stuff opaque, which means you can't figure out what it means, but still re-identifiable selectively. I think there's a lot of assumption. You can make data impossible to detect. People doing the analytics they cannot know who they're talking about or even what they're talking about, and then re-connect the dots just to the patient and the clinician.

You can get rid of all these data sharing agreements if you don't assume people have to trust each other, and you have to hold them accountable for bad acts if they're incapable of doing a bad act.

And when the Web came out, they wanted to do e-commerce. They didn't say let's do data sharing agreements

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

about credit card information as you send it across the Net. They just didn't do any e-commerce until they got transport level security, HTTPS, and suddenly once people started trusting it, you had all sorts of transactions.

But it's not because people trusted each other. It's because you built enforcement into the network that assumes that there are bad guys out there, and that patients don't trust various organizations with their data. Organizations don't trust each other with their various agendas.

So you have to figure out a way. How do we acknowledge that and still solve the problem? This is doable readily, easily, but it's -- you need a broader ecosystem. You need software innovators, for example, working with policy experts saying just what do you want it to do? Be very specific.

And you typically don't see those groups come together in government contracting processes, you know.

DR. McCLELLAN: Maybe more -- so more specifically teeing up the main problems that need to be solved would be helpful.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Jeff, you had a comment on that?

DR. BROWN: I feel like the 10th Amendment advocate up here, but I think it's important to always go back. Until there's a general and broad preemption, you have to look at the 50 states and some of them, no doubt, and I know it's frustrating to hear this from a development perspective, but there are more stringent sources of law. And right now, as it is, those more stringent sources of state law govern patient privacy.

SPEAKER: Not a problem.

DR. McCLELLAN: Let me go back to the microphones, and over here and then.

SPEAKER: (Inaudible.) Can I just -- one of this tension that everyone refers to the 20 public health and privacy has been addressed in a number of different countries, and that it would probably be helpful if the Sentinel Group also did an assessment across the world.

I mean, for instance, Denmark the linkage problem had been solved completely because everybody has an identified number, and it goes on every one of their records, and that's it.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And they've accepted that there so that there is possibilities of public action. There's this dual thing between the need for privacy and the need for proving the medical system.

Now I don't that the general population of the United States knows that about Denmark or knows that it's possible to have such linkages in an advanced democracy. It would be I think helpful to have that analysis.

DR. McCLELLAN: Are there international models to use here?

SPEAKER: Pardon?

MS. ROSATI: I think there are. I mean I think there's a lot of different countries, as you mentioned, that have tackled some of these issues. I think that they have an easier time of it than we do here in the United States because of different cultural norms and because they also have in many of these countries one -- they have a national health system with one payer, so it's very easy to store and aggregate that information and to mine it for useful public health purposes.

So I think some of the countries who have done it

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

already have an easier time doing it than we do here. But they might be very useful models to pursue.

DR. McCLELLAN: (Inaudible.) Great. Next.

DR. THORESON: Hi. My name is Richard Thoreson. I'm with the Substance Abuse and Mental Health Services Administration. This is 42 CFR Part II is our regulation. We've been at it for about 30 years. It works. It's built on consent.

And I would like to hear a little bit more discussion about patient consent, because if we're going to do the linkages you're talking about, if we're going to have people trust the system -- if I'm going to go to a doctor's office and share private information, which sometimes I do and sometimes I don't, and the -- and that's true with, I think, everybody -- almost everybody, even if we're willing to admit it. A lot of things that we would like to know about people, they don't share. We don't share.

So in the personal health record world, there's the potential there to capture much more really valuable information that a doctor knows. So what we really, I

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

think, should be talking about is gaining my trust, your trust, everybody's trust in the system so that -- and I think that's based on consent -- and I should mention that that basically that's what we're trying to do in HL-7 and at HITSBE, and we have a quite a very surprising kind of agreement amongst the privacy advocates and amongst the security people who are primarily concerned about protecting the interests of big institutions or of doctors or hospitals.

And when we started, we were really at each other's throats. And nobody thought in the security world that privacy consent could really work. I think now we're all working in the same direction, so it's quite striking that what we're working on in this -- there's a six -- I don't know -- three or four month effort sponsored by the Office of National Coordinator to come up with new privacy -- they call them -- I hate the word consumer -- privacy -- no, consumer preferences requirements.

And what we're doing there is working through all the technical stuff that Jonathan talked about and it basically be able to come up with a technology solution that involves consent that basically I can have my policies

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

about what my records could be shared and you could have your policies along with the State of Maryland or Shady Grove Hospital -- anybody can have their policies, and the security engines that are going to be out there -- not now, not with legacy software probably, but in the foreseeable and the vendors, big vendors, are really thinking about this, because we think that type of protection is going to be essential.

So even though it's not in phase one of the Sentinel Project, I think that being able to build in consent and giving patients much better control over where their data goes, then they might have much more trust, and you'd have much more -- much better information.

DR. McCLELLAN: Comments on that? Billing and consent or different levels of data sharing?

SPEAKER: As a practical matter, if you say, well, we'll include in our database only those who consent to have their data used, you bias the database or at least that's what the scientists tell me.

As a practical matter and one of the things I've sat here thinking about is whenever anybody says, well, it

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

depends -- a small cell depends on what's in the cell -- you make the system less and less workable. I think if you build in consent, the system would be less workable.

We're going to have to one way or another come out with broadly applicable rules that will apply across the board. We can't have every time there is a query, you know, the six or seven lawyers involved with the process debating, you know, what about this one, what about that one. You're just going to have to figure out some way to do this with broad rules.

DR. McCLELLAN: Other comments?

MS. McGRAW: I wish consent worked as well to protect privacy as people think it did. I mean I'm actually trying to explore the way that it works better in 42 CFR Part II to sort of understand, you know, practically how that gets operationalized.

But generally, all you need to do is think of the last time that anybody put a privacy notice in front of you and think about how clearly you read through it and how much you understood about what was really going to happen to your data. And it doesn't take long for you to conclude

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

-- maybe not all of you, but many of you -- to conclude what we've concluded, which is that it's a really lousy way to protect people's privacy.

I actually sat at a HIPAA Summit one time and had an attorney tell people, "If you're not sure whether you can do it under HIPAA or not, just ask people to give you a consent form" -- because they will.

So the rules are the most important thing. There is a trust built -- having said that, there is definitely a trust-building mechanism that patient consent can play a role in, and we're definitely exploring ways to allow patients to have some more control of their data than they do today.

But I guess I would caution: don't look at it as the sine qua non of privacy, because it doesn't in reality work as well as we would like it to.

DR. BROWN: By and large, de-identified data will work very well to identify signals, and it won't let us confirm any of them. And so before FDA actually hits --

DR. McCLELLAN: Can you expand on that a little bit? It won't work to confirm them --

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. BROWN: Sure. You can --

DR. McCLELLAN: -- because you need to go back to the underlying cases to --

DR. BROWN: -- right.

DR. McCLELLAN: -- look at the medical record and make sure --

DR. BROWN: Thank you.

DR. McCLELLAN: -- it's really the clinical situation that the summarized data suggests.

DR. BROWN: Right. Right. So, for instance, the example that Jennifer Nelson showed of MMRV vaccine and seizures. The signal was generated from de-identified data because it was all aggregated. And then the health plans went back and reviewed the records of the people who had seizures to see whether A, they really had seizures; B, whether they were really new onset seizures; C, whether they were febrile seizures and not due to some congenital anomaly.

And without that kind of checking, FDA will be in the unhappy position of accumulating a bunch of signals

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that suggest there might be a problem and not knowing what to do about them.

So my advice to FDA would be don't put yourself in that position of generating a bunch of signals, some of which may be real; most of which will be false.

So this is a terrific discussion. I just want to inject a sense of urgency, because I think there's very small space in which you can say start Sentinel off by looking just at the de-identified data, because it will very quickly to the agency and the public to a place that's worse than we are in now.

I mean it's one thing not to know there are a bunch of signals, some of which might be real and some of which aren't. But to have these signals and then worry about them and not be able to deal with them is going to be a very unpleasant thing to do.

DR. McCLELLAN: Comments from the lawyers on that?

MS. McGRAW: Yeah. And I'm -- you know, again, I'm much -- I'm a much bigger fan of the limited data set than I am of de-identification, because I think, you know,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

at least you've got, you know, some way to hold people accountable if they take data that they got for one purpose and then use it for another.

Now I get that the limited data set in and of itself is yet another sort of defined data set in terms of it has to have this identifier out and that identifier out and that identifier out. But at the end of the day, that concept of identifiers stripped out of data with an accompanying commitment to not re-identify that I can hold you accountable to, whether it's through a data use agreement or through some policy, I'd be fine with policy. I like policies.

DR. McCLELLAN: I think we have time for one last quick question.

MR. CESNACK: Arnold Cesnack, FDA Patient Representative. I guess I have the advantage here of not knowing anything really about the subject.

But it appears to me that there are -- I don't hear any absolutes in this discussion. I'm sure if you'll take your most protected data and give the CIA and NSA \$100 million, they'll decode it for you.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So it's a question of sort of how much effort is something they'll put into to get this. There are bound to be intermediate levels of protection. I'm not sure what they are. But you all that have been working on it should be able to put that together.

It seems to me that what's needed is sort of some definitions of the intermediate steps that everybody can agree on and then you would have to determine for a particular use how much protection is necessary.

DR. McCLELLAN: I think probably most people would agree with that. I mean I heard on this panel some discussions about, you know, taking Rich's point about the need to be ready to go beyond and be able to go beyond in at least limited ways completely de-identified data, thinking about a process to determine what specific identifiable elements are most needed and how those can be addressed and maybe Deven's notion of this continuous range of protections and handling it.

Any final thoughts along these lines as to how we go forward from here? Is that -- does that sound like the right general direction? Okay.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Alright. Well, I'd like to thank all of our panelists for a really interesting discussion. Thank you.  
(Applause)

DR. McCLELLAN: (In progress.) -- for me. While they're stepping down, I'd like our next panel to step up. This is a group that's going to discuss ways to identify the opportunities and challenges in building Sentinel so that it could support both FDA efforts to better assess the safety of regulated products as well as serve as a national resource for safety science, for questions that might be generated from places beyond the FDA that could be conducted by other government agencies and maybe by private sector entities as well.

This is an important question because, as you know, while FDA has a legislative mandate to fulfill in this area, there are a number of very interesting reasons - - and potentially very important public health reasons to make the Sentinel network more widely accessible to qualified safety scientists and analysis outside of the FDA. So that's what we're going to talk about now.

And to help us lead this discussion, we have Ron Krall, an associate fellow at the University of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Pennsylvania Center for Bioethics and former senior vice president and chief medical officer at GlaxoSmithKline; Arthur Holden, the chairman and founder of the Pharmaceutical Biomedical Research Consortium, and chairman, CEO, and founder of the Serious Adverse Event Consortium; also Fran Cunningham, the director of the Center for Medication Safety, and program manager for Pharmaco-Epi and Outcomes Assessment at the Department of Veterans Affairs; and Judy Racoosin, the Sentinel Initiative lead scientist in the Office of Medical Policy at the Center for Drug Evaluation Research at the FDA.

So a great group, and, Ron, can I ask you to start?

DR. KRALL: You can, and I will. Thank you, Mark. Thank you, Josh. Thank you, Sally, for the invitation to speak here today. I will try to be as succinct and brief in these eight minutes as I can possibly be.

My comments here are intended to explore what I think the necessary requirements are for Sentinel to be established as a national resource. And here, I'm especially going to discuss a pretty controversial area,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

which is the extent to which the regulated industry I believe can participate in Sentinel if it is created as a national resource.

My comments are informed by 25 years of working in pharmaceutical R&D and the development of new medicines, but most probably by the last several years of involvement in what has become OMOP and serving as one of the two pharmaceutical industry representatives on the Executive Board.

To explore what I think are the requirements for Sentinel to be established in a way that the regulated industry can participate, I think it's important to step back for a minute and for me to discuss what I think Sentinel is and what I think we need from it, because to the extent that our views about what Sentinel could be differ, we will come to different views about the value and cost of participation of the regulated industry.

So what do I think Sentinel is? Very briefly and you've heard this from many people already today. It see it as a collection of healthcare data that together with a set of analytical methods is capable of detecting important health outcomes.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

I see it as a complement to the observant practice of medicine that recognizes heretofore unknown associations of interventions with health outcomes; a complement to randomized clinical trials, to registries and other sources of medical evidence that inform us about intervention event associations.

I see some very classical uses for Sentinel: first, to rule out what are known as classically associated events -- drug-associated or intervention-associated events.

We know these events occur, and we know they're rare. We know we can't find them before marketing. And the question is can we detect them and how quickly can we detect them. Can we detect them better than in the setting of just observing medical practice.

Secondly, I see Sentinel as a tool to monitor or assess what I would call suspected associations, those that we have some suspicion occur, but are not certain they occur or are not certain of their incidence and are unable to calculate that.

And thirdly, to detect totally unexpected

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

associations -- those that have been potentially the source of most concern and are, in fact, behind the all by all comparisons that we've heard talked about earlier today.

If that's what Sentinel ought to be, what do we want from Sentinel? Well, we want validity. We want the ability or the -- the ability to be comfortable that the absence of an association can be taken as the association doesn't exist. We want reproducibility that the associations are detected reliably over time. We want a system that evolves, that improves. We want findings, new findings to inform the system, that is that new findings are available and they're used to improve Sentinel's ability to detect associations. We want a program of ongoing research. We want that research to understand the value of new data or the substitution of new data sources for old data sources. We want to be able to evaluate new analytical methods and their ability to improve our ability to detect associations. We will need to continue to explore new health outcomes of interest and our ability to detect those in Sentinel, and maybe most importantly, and this has been referred

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to earlier today, we need an industrial strength system.

Let me illustrate that a little bit more concretely. Suppose I'm the senior scientific safety officer in a fairly large pharmaceutical company. My company markets 40 drugs, introduces into the marketplace 2 to 5 drugs per year, 1 of which is a new chemical entity. If I just do some simple calculations about what I think I would want to be able to do, I can estimate that I want to do between 100 and 200 studies using a Sentinel-type system per year in order to be comfortable that the medicines that I'm currently marketing are free of those kinds of health outcomes that I've talked about. That, if you multiply it by the number of companies, begins to describe a very large system with tremendous capability. Now, we can argue about whether my numbers are correct, but even if I'm off by 10, a factor of 10, we're still talking about a very industrial type system that will be required in 5 to 7 year's time when our public expects that we will be able to use these kinds of data to assess the safety of medicines.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, with that background of what I think Sentinel ought to be and what I think its performance ought to look like, let me ask you to imagine a couple, and maybe three, futures with me depending on how much time I have left. So, let's imagine first, future one. Five years from now the FDA has successfully implemented Sentinel, a network of databases exists. The databases are all well characterized. The privacy of health information has been assured -- that's hard to imagine given the last session. Methods for interrogating the databases have been identified. OMOP and mini-Sentinel and other research efforts have determined that certain health outcomes of interest can be detected with a high level of certainty, others can be detected in some databases, not others, perhaps not consistently. Even others cannot be reliably detected at all, and many health outcomes of interest have not been studied.

Sentinel, in this future, is not available to the regulated industry. Now, on the basis -- in this future -- of certain findings in Sentinel, the FDA takes regulatory action on one or more regulated products.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

What is the likely response of the regulated industry? So, the skeptics view of the industry is that it will conduct poorly constructed, bias studies, spend a lot of marketing money to try to obfuscate and confuse the medical scientific community and protect its interests. The more likely outcome in my view is that a number of companies, let's call them enlightened and research-rich, will build their own unique and independent versions of Sentinel and employ them to label and direct use of their medicines, and to presage and influence FDA regulatory action.

Now, let me point out that this is what's happening today. There are companies that have invested in data, they have developed or adopted analytical methods, and begun using these tools to systematically study their medicines and there is even commercially available enabling software to do so.

A less likely outcome, but one that I might advocate to the industry, is that it bands together to build Sentinel II, investing collectively in a parallel system to Sentinel, capable of replicating Sentinel, but

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

perhaps even better, with more enhanced performance.

Now, in both of these latter outcomes, I predict genuine scientific disputes about whose results are to be believed, skepticism of the industry, Sentinel and anyone who chooses to work with it, and because of the industry's inherent interest in its performance, a lot of redundant research, a lot of redundant spending. So, what I'd invite you to do given that my time is up, is to imagine another future, and that is a future in which the regulated industry is able to participate in the building of Sentinel. And let me suggest that there are a number of ways in which that could happen, one of which is that it participates in the research backbone of Sentinel that develops validated reproducible results, methods, and characteristics of databases on which we can rely.

And the second is a scenario at the other extreme in which it actually conducts its research in the same system as other entities do and participates in a governance structure that guaranties the FDA primacy or priority of access to Sentinel, but also contributes

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

both financially and with expertise to the development of a system that is capable of meeting its needs. And I'll be glad to answer more questions about that in the discussion section. (Applause)

MR. HOLDEN: Okay, great. So, I've got eight minutes and I appreciate the organizers inviting me to talk about the International Serious Adverse Events Consortium. This is a nonprofit research organization that's focused on trying to understand the genetic basis of drug-induced serious adverse events. These are events that when somebody's on a drug, they have it, typically it's an immediate cessation of the drug, and so we've been interested in the genetic base of this.

I'm going to give you a summary of what we're doing so you can think about this relative to Sentinel. I'm not sure what Sentinel is really is, I'm not afraid to admit that. I think it's on the drawing board being drafted now. It reminds me of the UPS commercials where he's drawing and trying to figure out at the same time. But think about this as an example and then let's come back during the discussion and think, what are the types

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of capabilities Sentinel would have to do to facilitate this research?

So, the mission of this organization is to identify and to validate DNA variants that are useful in predicting the risk of drug-induced serious adverse events. This is a significant both public health issue and it's a significant issue relative to the productivity of the pharmaceutical industry.

This consortium has been put together as a -- essentially a privately funded organization principally using resources of the pharmaceutical industry in conjunction with the Wellcome Trust out of London, which is the largest charity funding biomedical research in the world and the efforts of this are strictly focused on the mission that I just got through. And the first phase what we've been doing -- and we founded ourselves about two and a half years ago -- our first challenge was to coordinate principally academic networks to try and get adequate numbers of cases and controls to do this type of research in two areas: drug-induced serious skin reactions and drug-induced liver injury,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and then to use the genomic methods to try -- that are available to us now -- to try to figure out, are there genetic factors that are available, that are identifiable, and could actually have some predictive power. And then the public aspect of this is that we make these research data, which are all obtained by consent and typical, not the type of research we're talking through Sentinel, but more clinical and medical research that consented, and we make these data, both clinical data, which are anonymized, as well as the underlying genetic data, available to research scientists that are trying to explore and to better understand these issues. So, that's the public aspect of it.

At the same time, any genetic associations that have any sort of strength, we're actually putting them out in the public domain so that they can be used free of charge and unencumbered down the road by researchers, whether they be in an academic setting or a commercial setting, and then also to try to facilitate certain types of challenges that we need a cross

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

industry approach, in this case defining a phenotype, defining a serious adverse event, what is it? You talk about signal detection, but unless you've defined what it is you're actually looking for, how do you know whether you've got a signal of A or B or C? So, us spending time really thinking critically about, what is the definition of various serious adverse events has been a focus. And then also to support the regulatory bodies.

In the first phase what we did is we basically have looked, as I alluded to in the top yellow bars, we established certain genomics capability where we didn't set it up within one organization, we picked the best and we developed a genotyping capability, a data analysis capability, and a data release capability in coordination, and we did our first two studies in serious skin reaction drug-induced liver injury. Unfortunately, I'm not going to be able to share with you the results, but I'll make a few comments at the end of mine, which will tie to Sentinel and what capability it may have in helping this research.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And then there are a bunch of other studies that we've been able to do because we developed this capability in other drug-induced serious adverse events, like torsade de pointes, angioedema. We're also piloting different new technologies to look more deeply into the genetics of things using next generation sequencing.

All the data that we generate is available to qualified researches that sign a data use agreement, to basically help us analyze or to pool it with other datasets that they may have, that may improve our understanding of the underlying biology of these events. And we do that through a website, which I'm just highlighting here, and there's a data portal.

So, this is a little bit of a complicated slide, but let me just comment here. The first phase of what we've done, we basically got across international investigators, academic specialists that were experts say in drug-induced liver injury, and we brought them together in scale, which had never been accomplished before, to look at these relatively rare events and then

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to match them with controls, genetically matched controls, to try and figure out what was going on. And so those academic networks have been our principle building block. There's also an opportunity that we've used to get cases from pharmaceutical company studies as well as begin to initiate pilots with some of the organizations involved in this room that have electronic health records that could help us identify and then enroll through traditional methods, these types of cases. So, we get more scale in terms of the diversity of drugs and the ethnicity of the patients.

So, this is an example of the first two studies. In a serious skin rash we put together a number of cases of drug-induced serious adverse events. This was in serious skin rash, principally Stevens-Johnson Syndrome, but aggregated cases from both industry as well as academic collaborators to get enough cases to do the study. Drug-induced liver injury, which we've done for about two and a half years, we've now developed one of the largest cohorts in the world by putting together academic networks, principally in

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Europe, in conjunction with company resources in order to do this research. And these are just some of the examples of some of the types of cohorts of different conditions we've been able to bring in from industry into this research.

Now, one of the things that we realized pretty early on, and it's been born out in looking at the genetics, the genetics are principally drug and ethnicity specific. It means, you need lots of different cases across many ethnicities to begin to try to understand what's going on there, so the opportunity to identify cases using electronic health records, and then enroll them to a traditional system, could be very, very helpful to us. So, we've done two pilots, one with SIRNA , the electronic -- EMR vendor, and we're working now with the HMO Research Network and looking in three different areas, and in the interest of time I won't be able to go through them, but they're these types of conditions that we've been studying to see whether or not -- what are the issues associated with identification and enrollment of patients in these

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

larger scale electronic health environments. And this just shows the details behind the one we're doing with the HMO Research Network.

One last point and then I'll just close with a few discussion topics that I think we can have relative to this.

So, standardization of the phenotype, even when we work with academic experts what we find out is they vary in the definition of what they think, for example, a case of drug-induced liver injury is, so we've put together an effort now, which we're running, and hopefully by the middle of this year we'll have completed, for an initial group of drug-induced serious adverse events. They tend to be the one that involve the immune system. So, we're including in this right now drug-induced liver injury, serious skin rashes, acute hypersensitivity syndrome, and we're working with expert working groups to define those to come up with a working definition based on their experience, the review of the literature. And we're holding a consensus conference in London that will be sponsored by the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Welcome Trust to kind of build this and we'll publish it. And the reason we want to do that is to put that out for the electronic health community so that there's a strong clinical definition so that when we think about systems and data ontologies and how we put this together, where we could track electronic health records, we know what it is we're trying to track.

So, just a couple of things to think about and we can talk about in the discussion relative to using EMR based identification of patients. A, I alluded to before. What's the phenotype or the clinical condition you're going after? If that isn't well-defined, it's very difficult to use this type of system to do this research. A, how compatible, if you have multiple electronic health records, how compatible are the ontologies and have you worked to put together a good system to map those? Getting variety across drugs and getting adequate numbers of cases across drugs and ethnicities, what we're finding is the genetics of this is varying more and more across different ethnic groups, so it means the scale of an electronic health record

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

system with many patients could be exactly what we need to do this type of research. That's the bad news. The good news is, is what we find out with as few as 50 cases within a drug or within an ethnicity, with well-matched controls, we can figure out whether or not there's a strong genetic contribution here. So, the feasibility of it from a genetics -- we don't need 2000 cases of drug-induced liver injury associated with Augmentin to figure out the genetics of it. Fifty good ones within an ethnicity and a drug and we've got it. So, that's important.

And then you obviously want the supporting genomics infrastructure and a good interface with that in doing this type of research. And lastly, are the partners committed? And one of the serious challenges that Sentinel will have, where you're putting together a lot of different parties, you're working on the architecture phase, we've found in our short history that some folks are really committed to move this forward and some aren't and you've got to get the people that aren't committed to move out and work with those

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that truly are.

So, that's my content. Thank you.

(Applause)

DR. CUNNINGHAM: Okay. My name is Fran Cunningham and I'm from the Department of Veteran Affairs. And when I was asked to speak on this topic today, I got a little excited because I'm often asked to present information on what we've done, so I kind of felt like a kid saying what Christmas means to me and I could say what Sentinel Initiative means to me. So that's the approach I'm going to take today so to speak.

So, just to review briefly the topic, it was opportunities and challenges in building Sentinel to support FDA efforts in evaluating medical products while serving as a national resource for safety surveillance conducted both by FDA, but also by other agencies in the private sector. And since I'm from a health care system, I will be speaking to you from a health care system point of view.

So, what is Sentinel to me? It's a continuous process, it's an iterative process. I look

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

at Sentinel as signal detection, in certain instances, signal strengthening, and of the best of all worlds where you can take pieces of it and use it for signal confirmation. That's my point of view, so that's the way I'll be speaking for the next, I guess, six minutes, right? Okay.

So, I'm going to briefly talk about challenges and I'd like to spend the majority of my time talking about the benefits of Sentinel if it were to be used as a national system.

So, from the challenges we've heard from many of the presenters today, all of the challenges or many of the challenges. I will not touch privacy. Being a data owner and also surveillance using my system for safety surveillance, I definitely understand the privacy issue.

What I will talk about is something I don't know was really honed in on earlier and that is, what happens in a health care system with signals when you've detected a signal? You're obligated to do something. A patient will ask, a provider will ask. So, what's going

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to have to be determined when Sentinel is used as a national system, is how do you act on the signal? When do you act on the signal? And what do you do with that signal? And from my standpoint, when we have seen issues, I used to say we could act on a signal so that we could provide appropriate use of an agent. I can promise you, it gets to a point where you just want to provide use of an agent, because if it's a signal out there that people are really concerned about, even if it's not confirmed, there are issues that need to be addressed, and so one of the biggest challenges may be to maintain use of that agent in, not this point in the given health care system, but in the masses, so to speak.

So, I'm going to go now from we know all of the known challenges and all of the known challenges have been addressed, not solved, just addressed, and so if they've been addressed, we can move forward.

So, what are some potential benefits? Well, looking at it from a health care system standpoint, if we have a national Sentinel system, then what we can do

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

is we can test signals that we've identified in our given health care system, in a larger system -- more rapidly and in the best of all worlds, more definitively. The same time, the FDA can address things that they may not have realized as a potential problem. Often when we speak of Sentinel we think of new drugs and new adverse events. What probably will occur will be common adverse events that happen in a given patient population that we didn't otherwise recognize at a national level.

So, let me move to the next major point, and this is, not that an agent is used and results in an untoward effect, but how an agent is used in a given patient population and results in an untoward adverse event that must be addressed. Having access to this national system would allow this to be identified more rapidly and, as I said, hopefully more definitively and conclusively.

I said I was going to leave challenges, I lied. I'm going to come back real quick to the challenge. So, here's a challenge. Here you have a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

national system and you're addressing a potential signal that's been identified in a patient population, and let's say at the end of the day, that signal was confirmed, but that signal was confirmed in that given patient population, in a given area health care system. That allows the health care system to act one way, the regulatory system to act another way, and the pharmaceutical industry or device industry, to act another way. So, what's going to have to be developed with this Sentinel system is some semblance of trust and understanding so that everybody can understand what their roles are with this national system. So, when I look at this national system, it's not everything to all people, but it's some things to some people and each of us needs to know what benefits us as a health care system, as a regulatory body, and as a pharmaceutical industry.

So, I'll finish with another area where I think the National Sentinel Initiative will be very good and that will be access by academicians and investigators, not necessarily in our discipline, not

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

necessarily sitting here or sitting here and not knowing what we're talking about. Many other disciplines have worked in areas like this and have advanced their areas, and so I think as this system becomes more nationally available, if it becomes more nationally available, we'll learn a lot more from other disciplines that we can apply from a safety for medical products and drugs as well.

Thanks. (Applause)

DR. McCLELLAN: Thank you, and thank you to our panelists. It's always useful as we think about the issues around Sentinel, to hear directly from our stakeholders, so thank you all for being here.

I think what we've just heard from the panelists reflects a lot of what we've been hearing for the last year and a half or two years from when we started, to really intensively plan and get going on the Sentinel Initiative, and recognizing from the beginning that this was an endeavor that could not be built without the input of all of our stakeholders who are here today. And I think Dr. Hamburg said it very well

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

this morning that we have to know when to ask for help and input of the people out there who know this area best, and as you heard from our contractors this morning, we have sought to get that expertise from those who hold it, so we've been very appreciative to have that input and are continuing to learn from that as we build this program.

I just want to touch on a couple things that I think, you know, directly came up from the panelists, one being recognizing that this is going to be a collaborative effort, but it's important that our initial focus be on meeting FDA's regulatory mandates. So Congress has mandated that we build this system to inform our understanding of post-market medical product risks, and so our initial focus is going to be on doing that to serve the regulatory needs, but recognizing that it's important that as we move that forward. And as we heard this afternoon, there are many groups and many stakeholders who are interested also in how this data resource can benefit them in helping them to understand the questions that arise from the point of view of the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

pharmaceutical industry, how it impacts their specific products that they're developing, from health care systems, how it can inform a better understanding of the particular safety issues that are rising in their particular systems, and from the research community about how this data can help to inform an understanding of the specific causes of these particular adverse effects so that sort of information can be taken into consideration as medications and other medical products are used in patients.

I know another issue that has -- that Dr. Krall raised was this concern that regulated industry be a part of this process and I think it's clearly important as we move forward that we will be working with all of our stakeholders, including regulated industry, to move this effort forward. And I want to just perhaps raise a point that we could discuss in a little more detail with regard to Dr. Holden's program of -- interestingly that the work on specifically understanding the pharmacogenomics of specific adverse reactions really relates to having specific cases. And

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we heard an extensive discussion this afternoon about privacy, and not releasing information, that, you know, is identifiable in any way. And so there's a slight tension between those two things of needing specific cases and not releasing privacy information. And I think perhaps one way to think about how these two interact is that through the work that Sentinel will be doing is to come to understand whether specific products are associated with the specific serious adverse events and if those relationships are absorbed, perhaps, then through the other -- through the consortium -- the SAE consortium has through its partners to work on those specific exposure adverse event pairs. But I think we need to recognize that in our best efforts to protect public health -- private health information, that it would be somewhat in conflict with what we're trying to do to identify specific cases. (Applause)

DR. McCLELLAN: All right. So this is a broad set of issues for discussion that the panel has come up with, and I would welcome people to head for the microphones for comments and questions.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

While that's happening maybe I could ask just -- this is maybe a definitional question. One of the main -- or an important requirement, especially as a result of the 2007 legislation, are post-market studies done by drug manufacturers of safety issues or related issues on their products. And just definitionally, as this applies to Sentinel, if the FDA asks for or requires a post-market study, but that study is actually carried out and funded and overseen, maybe in consultation with FDA, but it's carried out and overseen by the drug company, is that an FDA study using Sentinel or is that a company study? And if it's a company study, wouldn't it make sense to have it in Sentinel in a lot of cases? How does that fit into the definition we've been discussing? Should I have asked the lawyers on the last panel that question?

SPEAKER: Well, I think that there's -- I think there's actually some language in the statute relating to that if there is a program such as Sentinel, that the study is supposed to be done there and currently we don't have a functioning Sentinel and so we

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

are asking the sponsors to do those studies. So, at the point that we get to having a functional system, you know, we'll have to sort out those issues, but the -- I believe the language, to some extent, says it's FDA's job to do the study, but I think those details need to be worked out.

SPEAKER: With industry funding or --

SPEAKER: I don't -- Janet, do you know the details on that one?

DR. WOODCOCK: I don't have too much to add. We're just going to have to cross that bridge when we come to it. I think Ron raised a lot of the issues here. There are -- the statute says that if it can't be done this way, it has to be done that way. That's basically how the statute is structured. And right now, I think your point -- we don't have what Rich called the industrial strength Sentinel, so there is no way to do these studies that way. And the question is, can we develop ways to do such studies? And if so, then Mark's question, you cut to the heart of it, is then who would pay for those? How would those studies be supported?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, I think that's several years away so we can all kind of relax right now. We need to get the system stood up, but the point of this panel is, all right, as this program evolves and we get experience with it, then how do we contemplate using it most robustly for all -- different types of information needs that the various stakeholders have? And I think there are ways to do that. People shouldn't be in the audience imagining that the industry or Fran or somebody else, would run the entire system. We could do that in a way that would -- Fran, I would be happy to have you run the whole system, but what I'm saying -- or if there are -- whatever, that those folks -- there are models that we can work towards whereby the needs of other parties could be met by an independent group much as that might happen now when somebody contracts with Harvard or someone else to do some investigations for them. So, I think the answer is, we'll cross that bridge when we come to it.

SPEAKER: I can imagine a future, not very distant in the future, where the subject of discussion

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

between the agency and say a sponsoring pharmaceutical company, at the time, say six months before approval, would be how are you -- what's the program of assuring ourselves mutually that certain kinds of things don't occur as you introduce this drug? And that becomes a program of studies, some of which are Sentinel studies, that are agreed, mutually agreed, and carried out once rather than replicated or fought over for interpretation.

SPEAKER: Yeah, so in thinking about a Sentinel system and what sort of research you could do off of it, clearly what I'm surmising from the discussion here, that's kind of a first generation, which is a signal detection, let's see if there's an issue out there -- but given what we know, and I'll just use as an example the genetic basis of serious adverse events -- given what we're finding, and it's still very early in this area, it's really worthwhile for the planners, the people that are thinking behind what's Sentinel, how it's going to start and how it's going to evolve, to say, what types of research capability, given

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

its mission, should we be building into Sentinel, versus just saying, hey, we have a current legislative remit right now and we've got to do what we have to do to (inaudible). Now, I understand that.

But, on the other hand, if you look at this and you say, boy, we're picking up the types of signals you're likely to pick up with Sentinel given the size of clinical trials, and I think mostly in terms of drugs, but you could do biologics and devices, you're going to see a lot of the more common things. And what we're finding as we start to do these studies on the genetics of rare serious events is there are increasingly good examples where companies that actually have a product out in the market that you could say, hey, it has a safety issue, in fact, what it has is certain patients, select small group of patients don't respond to this drug. They have an unusual, atypical response. So, if we have a system that can identify that signal, how criminal would it be in terms of the public health and the productivity of enterprise not to try to figure out a way that you can do this type of follow-on research?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, my plea is, for those that are planning, think more about how you want this to -- think of the end, with the beginning in mind, as you start.

DR. McCLELLAN: Thanks. Let me start down at Judy.

DR. RACOOSIN: I'd like to thank the organizers for including this panel in the session because I think some really important questions have been raised, and I'd like to actually make a brief comment about what Ron Krall has raised here. I think there's just a huge elephant in the room that we don't really like to talk about very much. And if you look historically at what's happened, OMOP was started by the pharmaceutical industry as an independent initiative. Now it's very public and everything's going to be in the public domain. And some of the other Sentinel pilots have been started by academia. And I think the elephant in the room is that there really is a public trust issue here in terms of everyone wants the same thing. It's not like there are different research needs and different questions. We all want the same thing, but

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we're scared to actually admit that the scientists within industry, A, may have a lot to contribute, and B, that at the end of the day, they're liable.

FDA is also, you know, at the end of the day, the buck stops there, because they're responsible for assuring the public health. But it's really a shame that there can't be a process by which the collaborators could work together, manage the conflicts so that those with a particular private interest don't dominate decisions or dominate the process, or control the data, and it can't be one thing. I know, that's not a question, it's a statement, but I just had to say it because I've watched this whole thing happen. I keep seeing it and it's really a shame that we can't challenge some of the people who so fundamentally mistrust because of what some bad eggs have done, to let the best system come out of this.

DR. McCLELLAN: Judy, since you didn't ask a question, I get to ask you one. But you have a lot of experience managing collaborative and analytic processes and research processes, do you have any thoughts to kind

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of follow on your comment about how those kind of trust concerns could best be addressed?

DR RACOOSIN: Well, actually, Mark, you probably have the most experience in terms of the Reagan-Udall experience in terms of -- you know, as I actually took a stab at just looking at the description in the legislation about Reagan-Udall. I was really struck with how balanced the legislation was to try to control conflicts, and yet that didn't stop it from having some fundamental derailment from people that were fearful. So, you know, I would think that the expertise here is -- well, first of all, I think that the most important thing is to be truthful and to have these discussions openly instead of just pretending it's not there and then going down two separate, very expensive, duplicative paths. What Ron described is a huge waste of resources. For industry to feel they have to recreate something to validate something that was done because it was free of conflict, is insane.

So, I think it would be -- having these discussions honestly, coming up with a proposal --

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

developing the proposal to control conflicts, and then having these discussions with all the public interest groups that have the suspicions, openly.

MR. HOLDEN: If I might add because I've dedicated the last 10 years of my career in putting together very large scale, complicated research entities that have taken the best of the private sector, the best of government, and the best of academia to try and get things done in the public good, and that's a tough thing to organize. It really is. Because if you're an academic or if you're a company person or a regulator, or a provider in this case, nobody really wears the hat of responsibility. And I'd put forth that one of the things that can help us and it's the reason why I've done a few of these. As an example, if you have a focused organization that has a mission, that defines its values and says these are the policies that we're going to work and we're going to work in a specific area, for example, developing Sentinel in conjunction with the stakeholders, and then have focused, independent experienced leadership -- if you can

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

organize something like that, it's amazing how much you can get done. In some ways it's an accountability/responsibility/organizational challenge more than it is, I think, the mistrust and some of the other things that come up.

DR. KRALL: The FDA is the public health organization responsible and they have -- they span all the interests, right. And so this would be the one situation where we should be able to do it, and I'm involved almost full time in a public-private partnership with FDA with all stakeholders around the table of every stripe, and it's doable, and especially when FDA is sort of the convener and the responsible party. Even with all these privacy discussions, it is changed because FDA has the primary sort of central role. They're issuing the contract.

SPEAKER: I'll ask the awkward question then as the independent: Is there the right leadership in place to get it done? I mean, every entity, if it's in play -- I mean, to me, it's a bit of a circular thing going around here, but if you had the right leadership

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of that, you should have with the structure that you've organized. There should be a short-term plan, a long-term plan. I mean, is that in place or is that one of the challenges with Sentinel?

DR. McCLELLAN: Maybe Judy -- not to put you on the spot because I know there's a lot of leadership from FDA, but given the statutory and other issues involved here, maybe you could comment a little bit on -

-

DR. RACOOSIN: Yeah, actually, thank you for giving me the microphone here. I think there are a couple of things to keep in mind. I feel a little bit like as this discussion has gone into the realm of the Sentinel system being used outside of FDA, that there's a lot -- there's a sense here of using it for confirmatory studies to get the final answer on things. And I guess I want to distinguish that from FDA's expected use of it, which is that we're building -- I mean, we have the statutory mandate to build Sentinel and it's for active surveillance purposes and so it's to help us as an additional tool along with what we already

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

have in place, which is information coming from a range of other sources, which may be in CDER. It may be coming from clinical pharmacology studies or other post-marketing studies or adverse event reporting in the device realm. It may be coming from engineering studies, post-marketing reports -- I mean, there's a range of sources from which we get information that's then factored into regulatory decisions that are made. And Sentinel will provide another source of information for that to help point in what direction the agency needs to go, and whether if that is that we need a more formal confirmatory type of study, FDA, each of the centers has in place contracts with various organizations to conduct those sorts of studies.

And so, I think, it's important to recognize that this is a tool that we're building to help us understand, and closer to real time, particular safety issues for which we don't really get good information now. And it may -- what we envision this as is really complimentary and augmenting what we have currently in place. So, maybe adverse event reporting is as good as

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we're going to get for these rare bad things that happen because maybe in 20 million or 50 million people, you only still have a relatively small number of people who have been exposed to a less commonly used drug and have a rare outcome. So, maybe we are -- I mean, we anticipate that we're still going to rely on the adverse event reporting system for rare, bad outcomes, but that Sentinel will go a long way in helping us with the things that commonly occur in the background that we don't get reports from. But now we'll have a defined population in which we can evaluate these commonly occurred issues with appropriately control groups.

So, recognizing what it's going -- you know, I think the thing that's important to recognize as we're building this is -- and this is something that's going on internally in FDA is, what can Sentinel actually help us with, and what is it not going to be so helpful for and to understand that we need to keep building Sentinel for the things that it's going to be able to effectively help us with. And we need to build other expertise and structures in place to help us understand the things

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that it's not going to help us with.

So, I think understanding that this is a tool that's going to inform, but not in and of itself as the only tool that we have, that, you know, we're going to incorporate this into the processes we have internally for making decisions about post-market safety issues. And I think that is distinct from what a lot of this discussion is around, which is how can outside organizations potentially use the Sentinel system? And I think these are all important points that are being raised. And I think, you know, as we get practical experience with many Sentinel, with the learnings from OMOP, with our federal partners collaboration, we will be able to more effectively see how potentially Sentinel could be expanded for other users.

DR. McCLELLAN: So, more to come. Next question?

DR. O'BRIEN: Thanks. I'm John O'Brien from the College of Notre Dame, School of Pharmacy, and specifically of the squishy discipline of social and administrative sciences, which at Hopkins they called

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

health behavior and society. This is a fascinating panel, especially as it relates to the topics of patient engagement and personalized medicine, and recognizing the limitations of what Sentinel can and was intended to do, and sort of the Sentinel, too, that you described.

I'm trying to get my arms around whether or not the public will be able to -- or whether we'll be able to stem the demand of the public who actually wants to access the dataset in the way that you described. When the law passed in 2007, when we were together last year, I didn't know there was a website called Patients Like Me. And Patients Like Me is now reporting that the incidents of problem gambling in patients taking anti-Parkinsonian medicine is now 13 percent, which is much higher than the original sponsors were allowed to put in their label. So, it's interesting that regulated industry is not allowed to say something about their product, but yet sort of brand new websites and potentially even bloggers and others that repeat this information are.

The concept of whether or not a drug company

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

is allowed to sell me a product based on what information they may have gleaned from a database or bought from purchasing a database company is almost balanced by whether or not the drug company has the right drug for me. And as more patients are starting to understand their genetic profile and starting to come into pharmacies with data from Roche's AmpliChip and all these other questions, I think there's going to be a real interesting challenge on the health professionals who know that this information is out there or this information is being discussed in some circles, but yet have no way to access a sort of validated, regulated, overseen set of data that could actually be used to answer these questions. Especially this panel up against the backdrop of the privacy discussion, there's almost not a -- in addition to the is it okay if a life insurance or a health insurance or an employer models my health and financial future, there's almost the patient in the family saying how can we budget for our health and financial future, especially as we get more into this consumer-driven, pay for performance, patient-

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

centered, community-based, participatory research, everybody coming together and the medical journal going away conversation.

So, recognizing that this is more of a what-if conversation, I wanted to say thanks for putting this panel together and, again, get your thoughts as to whether or not the law will be able to keep up with what is already starting to emerge as consumer demand for how their pharmacogenomic data or how their health professionals can use or predict how that data will affect their health can ultimately be used.

DR. McCLELLAN: Any further comments? I mean, what -- as people become more involved with their own health information, to the extent that their data are contributing to the Sentinel network, aren't they going to expect some kind of way of figuring out how their -- what the network means for them, if there are any medical ramifications?

SPEAKER: I'll take a crack at a comment. I can imagine a governance structure for Sentinel where the FDA certainly directs its use of Sentinel to study

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

important questions has priority access to the resources in order to conduct the things it needs -- the studies it needs to conduct to fulfill its regulatory mission, but that there is a broad representation on a governance board that sets research priorities that includes those that are of interest to health care systems, patients, physicians, as well as the regulated industry. Don't pretend -- I don't pretend for a minute to know exactly what that construct looks like, but I can imagine that one could be developed and a set of priorities established for important research that uses the Sentinel infrastructure data sources analytical methods.

DR. McCLELLAN: Are there any examples -- I mean, OMOP has been mentioned a couple of times. Are there any examples of governance structures that may not be exactly what should be used here, but might provide some useful insights or lessons?

Arthur, I know you've had a lot of experience with this.

MR. HOLDEN: I'm not sure about -- it would have to be independent. I like the idea of having the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

parties that really have a vested interest in thinking both short term and longer term coming together under some structure, but it's got to be a group that would have, you know, the appropriate cross-disciplinary experience. I'll just give you an example that I thought of as you were going through your scenario, which was that even though we're early, we're already seeing genetic risk alleles that, depending on the person and the drug they're exposed to, in one patient it might cause an incident of drug-induced liver injury based on a drug exposure in another, in that same patient, if they were exposed to Abacavir, they might have a hypersensitivity reaction. I can envision risk alleles that everyone should be aware of that this consumer-oriented world will be saying, well, jeez, do I have these? Or if there's a new event tracked by Sentinel that comes up with a signal, they're going to say how does this relate to some of these broader risk factors? And if you're not willing -- if we're not thinking about that, at least initially now, we're really not putting together -- to use a phrase that's

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

popular in Washington, we're not connecting the dots.

DR. RACOOSIN: Yeah, I was just thinking about some of the things that when you started your comment you were talking about how the incidents of pathologic gambling is much higher as reported on certain websites than in labeling. And I think it raises a couple of issues that -- to think about, well, how are signals going to emerge for evaluation in Sentinel? And I think one of them is that -- and I think someone this morning talked about how patients don't tend to always talk about things to their doctors that might be important and, you know, pathologic gambling is one of those. And I think the sexual side effects with the SSRIs is probably another one that the, you know, percentage in labeling probably doesn't match what's in the literature as people have observed over the years.

So, there's always going to be adverse events that in clinical trials people aren't going to be willing to talk about that are going to emerge when people are out in the community using these drugs and

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that will emerge either in -- as reports to the adverse event reporting system, as discussions on websites. And I think it raises issues about how best to understand those signals that are coming out of those sources and how can we connect to this new way that people are communicating to understand what those signals are. I mean, we pay attention to the consumer reports that come into the adverse event reporting system, but, you know, clearly there may be other ways to connect into these various networks to better understand things that might be coming up that, you know, people aren't talking about in sort of traditional venues. And so, you know, ultimately that there are pharmacovigilance groups within the agency that work on these signals that are emerging, and at some point it interfaces with what Sentinel is doing.

But that was, I think, what struck me in your comments was, you know, how are we learning about these signals that maybe people aren't hospitalized for certain things? But these are, you know, important adverse effects that are, you know, affecting people's

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

lives. So, that's what -- I just wanted to respond to that. Maybe that as we move forward, you know, we're not just -- you know, we are not -- you know, signals are coming from many different places and we need to be in tune to where they're coming from.

MR. HARE: Jonathan Hare, Resilient Network Systems. One observation about networks, what makes network work is it's got to be -- this is especially true for very large-scale networks is they have to be general purpose and not make any assumptions about (inaudible) why you would want to have a network. So I like the way that the Sentinel network was originally conceived which says this is not our network, we're just essentially an application on top of many different networks.

And patient safety, if you really think about it, the people who have the data and the users you need to connect with, patient safety is not their primary focus. So, they're very unlikely to participate and get the kind of scale you need unless you can serve their agenda.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, if you think about, you know, what does PhRMA care about? PhRMA loves drug discovery, right. They really love medication adherence for their drugs. They like patient safety as long as it doesn't yield false positives and/or yield blunt trauma, kind of regulatory interventions, if you can satisfy all those criterias on board. Doctors like to get paid conveniently, they like to save them and their staff's time, and they don't like liability. So, figure out, how do you fit into what they're trying to do? Link these networks together, otherwise you're really not going to get the kind of adoption.

Think about somebody creating a cell phone network and they say, but it's just for safety. You can only use it to call, you know, 911 for fire or police or whatever. What are the odds that everybody's going to have a cell phone, know how to use it, keep it charged up, be in the habit? It just wouldn't happen.

Now, to make that possible you have to come up with a governance mechanism that does not assume consensus, that nobody really controls it, so everybody

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

is participating. Whatever your policies are, you can enforce them.

And secondly, the ability to, without creating a burden on whoever is releasing the data or consuming information, enforce all the other policies that have to be enforced that they don't even want to know about because, otherwise, they're just saying, oh, we're creating liability or somebody's going to get after me for some reason. So you have to come up with governance mechanism, sort of a neutral Internet-style governance mechanism, that can provide that kind security. If you can do that -- and I think what I would suggest for the Sentinel initiative is since everybody else is now creating networks, reach out to them as soon as possible. They all have the same problems, they need the same data, the same kind of transformations, they deal with the same dirty data problems, they need to reach the same users, and try and link up with them since you have a head start, and come up with pragmatic solutions to meet all those issues.

DR. McCLELLAN: Sounds simple. That's

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

actually a good transition to our next panel. But before we wrap this one up, I'd like to ask those of you on this panel any thoughts or reactions to Jonathan's comments about how to sort of make the governance here more self-executing and reinforce support for the post-market active surveillance activities at the same time?

SPEAKER: Make a specific comment about -- to the extent that the regulated industry participates in Sentinel or any portion of Sentinel, I think one of the lessons of OMOP and one of the lessons of a number of the other consortiums that have been public-private partnerships for the regulated industry is the willingness to accept a minority and even a tiny minority participation in that governance structure, and a willingness of the rest of the community to recognize or at least accept that that participation does not, per se, mean that the governance is somehow conflicted and therefore impossible.

SPEAKER: You know, I think this gets at why we have the Federal Partners Working Group because I -- we've got AHRQ, who are awarding contracts related to

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

distributing networks for comparing effectiveness research, which we're going to be hearing about, I think, and there's the VSD, the Vaccine Safety Datalink, part of the CDC contract with members of the HMO Research Network for vaccine safety. And I think, you know, part of trying to understand the best way to move forward is really to work closely with our federal partners because maybe there is a way to do this in a very efficient way.

MR. HOLDEN: One comment that I would add is that this is really a complicated set of multiple agendas and I think that it's worthwhile for Sentinel to be organized with a very specific purpose, thinking about how it may want to evolve. But, for example, the International Serious Adverse Event Consortium in its second phase, which is now being funded and will be executed over the next three years, we'll be working with a number of the units that you had won in Sentinel, for example, the HMO Research Network, some of the larger electronic medical record vendors, experimenting how we put together systems that will enable this type

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of broad-scale surveillance and then enrollment of subject in the follow-on research.

And we might just want to just stay in touch and coordinate because we're solving a lot of different problems that Sentinel doesn't have to deal with right now and vice versa. And maybe part of what we want to think about with these meetings as this evolves is what are some of the collaborative efforts that run in parallel and how do we think about integrating, if at all, as they both progress?

DR. McCLELLAN: Thanks. Well, I'd like to thank all of our panelists for a terrific discussion on a very interesting and broad topic.

It is now break time. We are going to reconvene at about 3:30 for our final, great panel, which is on an even broader topic of how Sentinel can fit into other network and better evidence activities.

(Recess)

DR. McCLELLAN: All right, everyone. We're going to start again with our final panel for the afternoon. And we certainly saved a very interesting

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

topic for the finale.

Our final panel deals with the intersection between medical product surveillance and other uses of the same types of health information. So, coming up right now are our panelists to lead this discussion.

That includes Dr. Carolyn Clancy, the director of the Agency for Health, Research, and Quality. We are very pleased that Dr. Clancy is able to join us this afternoon. She has a unique perspective from her position at AHRQ and her experience in the general area of developing better evidence on the kinds of infrastructure that are around and that are coming, support many enhanced uses of health information.

Carolyn is going to start us out with some relatively in depth remarks, and then after that we're going to hear from Dr. Paul Stang, the senior director of epidemiology at Johnson and Johnson, and the co-principle investigator of the OMOP project, which has come up repeatedly today for some of his thoughts on this issue.

And then finally, Dr. Rachel Behrman, the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

acting associate director for medical policy and a real force behind many of the FDA's science initiatives in the drug center. And she's going to add her thoughts as well. And then we'll of course open this up to discussion with all of you.

The question that we've put to this panel is, what challenges need to be addressed to create a distributed network, a network that can be used not only for answering questions related to safety surveillance, but also for other types of public health and biomedical evidence questions. Comparative effectiveness research, quality measurement, and the like.

This question is motivated by the fact that the data, the infrastructure, and the methods upon which Sentinel is being built overlap substantially with the needs of many of these other areas of evidence development, as has already been noted by many of our participants today. And there are a lot of activities underway already simultaneously having to do with these other purposes.

A variety of federal initiatives are focused

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

on developing multipurpose electronic data networks to promote the enhanced use of health information, both in the deliver of care -- both to facilitate decision-making about individual patients, and for secondary uses like the one that we've been discussing today.

So, as Sentinel moves down the road, is it possible and practical for it to be designed to work with these other pieces of infrastructure to -- as I think Jonathan commented on in the last session -- to build on or promote and support the networks that are already out there and that are being developed further to support some of these other uses.

Carolyn? I'd appreciate if you could go ahead and start us off. Thank you.

DR. CLANCY: Thank you, Mark. And good afternoon, everyone. I guess those bells are calling you back from the cookies and coffee. Just waiting for the slides.

Now, I understand that all day long the conversation has repeatedly come back to one of Mark's favorite topics, which is can the -- can we have a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

common infrastructure that supports comparative effectiveness research, surveillance for adverse events, and quality measurement and improvement. And I think the short answer is, yes. And all of the action is in, how do we get there and what are the steps moving forward. And I don't pretend to have all of the answers.

But from the perspective of an agency with a big stake in comparative effectiveness research, I certainly have some thoughts to share.

So, just by way of a few comments to set the context, this is just a quote from Andy Grove. When he had prostate cancer in the mid-'90s, was incredibly struck by how little good comparative information there was about medical treatments or about where to get them.

And if you think about it, anyone you know or you yourself would want to know, A, what's the right treatment and, B, where should I go to get it. And yet, for the most part, that's magical.

That doesn't mean Google won't give you 5,000 hits if you try to type in some kind of question, but we

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

don't really have good data yet. And I think that need and the interest in that information is going to drive a lot of development of future networks.

Obviously, this all occurs in a context of health reform where we're trying to figure out, how do we get to a system, ultimately, where all Americans can be confident that they receive high quality, affordable care. Even though we don't -- we still have a lot to learn in terms of how to achieve that.

But all of this means that the common infrastructure that we're talking about is what the Institute of Medicine and others often refer to as a learning health care system. In other words, every day, huge amounts of information are generated as a byproduct of providing clinical care.

The problem is, most of it goes actually nowhere. With greater adoption and increased advances in the sophistication of health IT, as we begin to see products that support a system that rewards value rather than volume, we will have the potential to build this network.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

But make no mistake, this is going to require lots and lots of collaboration. Not just between AHRQ and FDA or between private funders or between health care organizations, but virtually all stakeholders.

So, just a few words about comparative effectiveness and translating science into real world applications with some comments at the end about where do we go from here.

ERA gave AHRQ -- or, actually gave HHS \$1.1 billion. And you'll recall when the recovery act was winding its way through the Congress, no matter like how schematic the overview was, where's all that money going, that 1.1 was always mentioned.

Anyway, 300 million to AHRQ, 400 to NIH and 400 million to the Office of the Secretary.

Now, the Congress was wise enough to ask for two major inputs into how the Secretary's money would be invested. The clear message from the Congress was that they wanted to see a coordinated, integrated set of investments. Which, didn't mean that we all had to walk in lock step together, but that the entire portfolio

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

would make sense.

At the same time, they recognized the urgency of making the investments as rapidly as possible. So, the two major inputs, one is the Institute of Medicine, which came out with a list of 100 questions based on extensive stakeholder input, and I was really very, very excited as were many people on the committee that Mark was part of that.

And their list of questions is actually on the IOM website. It's actually kind of cool.

The other was the federal coordinating council, which drew on scientific leadership across the department, and actually set the stage for investments in comparative effectiveness as one of the leading foundations or pillars, if you will, of the scientific infrastructure that we're going to need to make health reform sustainable.

It's not CER by itself, it's CER, it's health IT, it's investments in prevention. And that's not the end of the story, but the recovery act really did set the stage for beginning to take advantage of all that

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

information that's generated every day, even as we're sitting here in medical practice but we don't take any advantage of.

So, what we -- who we had on the federal coordinating council were scientific leaders across the department, both those involved in CER as well as folks from veteran's affairs and defense. And in addition to that, people representing agencies like FDA that are very much interested in and share a common interest in the methods and applications of the scientific methods for adverse event surveillance or other applications. And also, leaders representing the needs of priority populations.

So, this overview for those of you who like schematics, gives you some sense of the framework by which we're thinking about our investments in comparative effectiveness research. From horizon scanning, which no developed country as far as I can figure out, has managed to do very well systematically. In other words, what's coming down the pike in the next three to five years that we should be anticipating now.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

In terms of getting the best possible information, identifying needs for evidence, generating new evidence, and very, very importantly, disseminating that information to people so that it's available in a real time way. In other words, that makes the right thing to do the easy thing to do.

I'll say that again. Because it's never the easy thing to do. The right thing, the easy thing. Okay?

So, the focus on the \$400 million to be allocated by the Secretary, we got really some terrific input from multiple stakeholders through listening sessions, lots of online comments, and so forth. And a very key insight was that this was an enormous opportunity to make a one time transformative investment and infrastructure.

And so what I'm showing you here on the slide are some of the areas where you will be seeing more and more announcements over the next couple of months. In data infrastructure, including distributed data networks. In dissemination, because we don't know how

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to do that very well. We still have quite a translation lag from the time science is published to the time it actually becomes a routine part of practice.

And to making sure that the gap between our aspirations to address the needs of priority populations -- I don't mean just members of racial and ethnic minority populations, or people of lower socioeconomic position. But also people with multiple chronic illnesses, people with disabilities, and so forth.

We always aspire to have a diverse representation in clinical studies. The -- but the actual achievement or execution sometimes falls short of that aspiration. So, those are the areas where we're making the lion's share of investments with the Secretary's money.

Now, what about distributed data networks. You've been hearing about these all day long, so you're waiting for me to tell you, here's the app and you can just plug right in and you and all your buddies can share electronic health records.

We will be investing on behalf of the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

Secretary and building on two prototypes that I know you've heard a lot about because I know Rich Platt was here speaking earlier today. Three electronic health record distributed data networks that will include linking clinical and administrative data. Because clinical data, absent admin data, is not going to get us all the answers that we need.

The funding will be used both for infrastructure support and to test the ability of networks to answer relevant questions.

A lot of this is very, very basic, common definitions across multiple organizations. Sounds really, really easy until you actually start doing it. But the power of that, I think, is really incredibly and it's certainly that power which has inspired Janet Woodcock's leadership for Sentinel for the past several years.

I was telling someone earlier, I have dog-eared copies of the transcript from your public meeting a couple of years ago.

Clearly, there's a huge synergy here between

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

comparative effectiveness and health IT. That said, this is a road that needs to be built. Electronic health records designed to support a system that rewards volume do not automatically lead to better research data. That's going to have to be built step by step, element by element.

These are just the operating plan set of principles for AHRQ's investments in CER, I won't belabor that point.

These are some of the examples that we're making a big investment in registries for those of you whose -- either yourselves or your colleagues are exhausted trying to respond to the prospect deadline, which was extended just a tiny bit.

And we're going to be launching a citizen's forum in the next couple of months, which will help multiple stakeholders engage in a very important series of dialogues about what is comparative effectiveness. And I would fully expect that that will be an opportunity to look at these other common applications of the same sorts of scientific methods and data.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, just to give you a sense of the two prototypes that we invested in. And I know you've heard a lot about the HMO research network. The other prototype was Dartnet in Colorado. These are small practices, by which I mean not small people in them but a small number of clinicians. Providing care and primary care, working with a couple of hospitals. And very, very different approach than trying to integrate and try to make harmony and peace, if you will, among multiple bureaucracies.

This is very, very different -- we thought it was a very nice contrast. And I think has given us a very clear sense of what's feasible -- Annals of Internal Medicine, early September of '09 has some very nice descriptions of both networks.

One other one I just wanted to mention, since this is adverse event surveillance, we're talking Sentinel. We also worked with primary care networks to try to figure out, could we create and work with them to develop a web-based tool which -- where they could report both on medical errors and on adverse events.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And that was very, very successful -- part of it was noticing and believing that many of these same practices were unlikely to be contributing much to our knowledge through MedWatch and so forth.

I will say this, though. Adverse events much, much, much less sensitive than sharing information about medical errors. But we think this was a very nice leading forward.

So, where do we go from here? First, I think there are enormous synergies -- and you've been hearing this all day. Both in methods and in infrastructure. And I can't overemphasize methods.

Mark said something to me the other day to the effect that you know, pretty soon, anyone's going to be able to get their hands on a very large database and everything statistically significant -- so, the real challenge here moving forward together is going to be not discussing the idea -- should there be synergy, of course there's synergy. And huge overlap. But how do we advance the methods even more rapidly and as well as the data infrastructure and so forth?

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

The distinction between the comfort that people had or the sensitivity around sharing information about errors, versus adverse events. I think underscores the points about clarifying governance or, rules, if you will, for learning health care system for different applications.

People are likely to have very -- go into very different applications with a different sense of how much they want to share or how much they want to make certain that they understand the terms under which the information that they generate will be used.

And I -- we also clearly have to anticipate unintended consequences. And if there is one key rule that we're all going to have to learn -- I mean, have to apply over and over, it's incentives for participation, okay? If we ask people to submit data to a dark hole, they won't. They have too much to do, they have day jobs, they really don't need other tasks.

So, the question, I think we've always got to keep in mind is, what's in it for me? For the people that we're asking to share data and make judgments about

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

what's reportable and what's not. For the physicians in the Colorado project, this is quality benchmarks. Really, really important.

But I don't think we can ever, every underemphasize incentives for participation.

So, with that, let me thank you for your attention. And I'm looking forward to the discussion. (Applause)

DR. STANG: Thank you. Wait for the slides to get up. I appreciate those of you who have been here all day. Staying even longer, especially those of you not related to me.

I'll start with a disclaimer. I've kind of gotten used to doing this, but I want to make it clear that these do not -- what I'm going to show to you are themes that you've heard all day long. They don't necessarily represent the organizations that I work for, J and J in particular and OMOP, as you've heard.

But I have gained a lot of insight from the last couple of years in working with OMOP. And that certainly influenced some of the things that I'll talk

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

about.

One of the ways to think about this whole world of using data to look at issues around safety and effectiveness is -- and this is just a simple kind of way to think about it is -- you're looking at the intersection between the tools and the methods you're using to measure whatever that effect is, what data you're using to make that assessment, what the target disease is -- we can all imagine that those decisions around benefit and risk differ by what the target illness is. Cancer patient is making very different decisions about that balance as opposed to somebody with migraine headache. And all that differs somewhat by perspective, whether you're a payer, a clinician, a family member.

So, I just want us to keep those kind of outlines in mind.

Am I going forward or backward -- there we go.

So, I'm breaking this up -- this brief talk -  
- into three sections. One's the data, second is the

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

issues around the evidence, because we were encouraged by the pre-work here to think about the issues in doing this kind of work. And finally, it's the people involved in the work.

First, we've been hearing all day about all the rich data that we've had. I go back in this field probably about 25 years and I remember in the '80s having meetings where groups of people got together and talked about the one or two data sets that were available to do research. And it was pretty exciting, and there are monographs that, if you go back to those times, it was kind of interesting.

We've certainly come a long way. There's no shortage of data, as we've been hearing all day. It's - - may not be the right data, though. Everybody's generating data, and we want to be careful that the data that we're using is the right data. For what we're trying to measure.

So, we want to think about things that we've heard about again today: quality, completeness, credibility, and transparency. And I'll try to touch on

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

those very briefly.

When we've started to look in OMOP -- and a lot of this has been work Patrick has been doing about -- you can have 100 million lives and it just starts dawning on you, you can 300 million lives. But if you don't have enough people on the drug that you want to study, it doesn't matter.

You can have billions of lives, but you've still got to have enough people if that's your focus -- so, let's not rest on our laurels that we can accumulate or get our hands on hundreds of millions of people, the key is to be able to get our hands on the right people. And the right data about those people, and I'll get to that in a second.

There's other dichotomy -- people refer to it in different ways, but risks -- at least the risks we study, tend to be very clinical. They tend to be represented fairly well in the clinically types of data: aplastic anemia, stroke, myocardial infarction.

Benefits, on the other hand, depending on how you define a benefit or effectiveness, can be things

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

like productivity; can be things like reduction in blood pressure; can be things like, mobility, activities of daily living, which, frankly, aren't very well captured in the data systems that we're working with today, certainly not systematically captured if they are. So, there's this information difference between the risks and the benefit side that that's ultimately the decision we're trying to make, is trading off risks and benefits.

We have a lot of issues around definition of these types of things, and that's been talked about all day long. I've been involved in the OMOP side on definitional things, and frankly I'm kind of sick of it at this point. But we went out to a large number of people to define the 10 events of interest. And we ended up with -- what -- 40 -- 35 different definitions for those 10 events.

And we were going to be testing all of those. So, there's no consensus on how to do this, certainly.

And can we be very transparent about all the characteristics in a given database. It's also come to light -- and I think some of us already realize this --

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

that not all data holders can be, for business reasons, or want to be totally transparent about everything in the database.

You know, some of them represent insurance plans, there are benefit design, business issues, and there's all kinds of things that might give them pause to be totally transparent about how their data get used.

This is an example of some of the definitional issues. This is a study from Canada, where they simply applied seven different credible definitions of dementia in exactly the same population. And you see that the -- see if I get a pointer here. Yeah, you see that the prevalence of dementia varies from about 3 percent to 30 percent in the same patient population, all with very credible definitions.

That's kind of a wild example of the kinds of things you can get into, but needless to say, you can get into a lot of issues if not everybody agrees. And frankly, you don't know which doctors may be applying which definitions when they sign the patient out as demented.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

The other thing gets to some of the quality issues that we don't often see in these databases, and here you might see a patient who's filling with great regularity their prescription for their inhaler. But, in fact, they're using it incorrectly. But we can't see that in the data. And that's, again, a delivery of care or a quality issue -- a patient education issue, whatever you want to call it.

So, let's talk about evidence.

We talked today about some very big problems, or some very big issues that we need to tackle. It was hinted on in one of the -- oh, my god, I've got to rush -- hinted on about what are we calling credible evidence to make a decision. And that's really what I'm getting to here, what is the endgame that we're trying to affect? Are we trying to affect labeling, a change in behavior on the clinician side, so on. So forth.

And finally, who is involved. You don't want to do this on your own. You do want to engage everybody that you can possibly get who has a reasonable viewpoint, and reasonable ability to contribute. There

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

are going to be conflicts of interest, they come in all shapes and sizes, and the key at the end of the day is trying to develop a transparent process. And we did talk about funding briefly.

But no two groups are going to see the things the same way. No matter what you do. That's just human nature, everybody sees things differently.

This is actually a birthday card from my older brother. (Laughter)

We need to think longitudinally. For instance, can good surveillance methods actually predict the outcome of an evaluation study? The tension between comparative effectiveness, which is a population normative kind of approach, versus personalized medicine, which is very precise and very small. And I think is a huge issue.

We need to think in terms of processes, and we've been talking about industrial strength processes, I definitely think that's part of it. Dr. Clancy just mentioned again the idea of a learning organization, which I think all of us want.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

The need for continuing training and education of the people that are going to use this data. I think is something we haven't talked a lot about, but I think we all agree is very necessary.

So the next steps -- this is my last slide, I think -- invest in the basic science behind the science. We've been talking about methods, and processes, and definitions. It's kind of boring stuff, but at times -- but it's the necessary first step. What are the standards on the data side. What are our evidence standards going to be so that this data can be credibly used in the whole decision-making process, what is the process itself, what's the governance structure, which a couple of panels have addressed, and where are we going to go for education and training.

Finally, a quote from Harry Guest. Those of you who know it, which I think kind of encapsulates my thinking here: It's important to know what you don't know, but could.

Thank you.

DR. BEHRMAN: Okay, so I have the privilege

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

of being the last before Mark wraps up.

I'd just like to add my thanks to Mark and to Josh and to Sally, and their colleagues working for really very -- invaluable help over the last 20 months. And to many others in the room, who every time we've asked, could you please -- everyone has always said yes. And that is really the main point I want to make.

I'm usually by the -- at this point in the meetings on Sentinel, I'm usually the one holding my head in my hand and moaning. And I'm not doing that today. Because if the -- there's actually have been four Brookings meetings, if everyone remembers correctly, right. And I -- the first two were very diffuse. And if we also look back, the first two -- there was, I think, only one member regulated industry - - at least I remember that distinctly at the second one.

Last year was very interesting, but again very much fact-finding. And if you think about the conversation this year, it's been far more targeted with not only presentation of data that have been developed, but a real sense of a path forward.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So, in focusing on the question for this panel, which is, what are the challenges, I'll just give the answer first and then say I've developed -- the challenges to continue the very measured, thoughtful approach we've taken today in a very transparent way. Because that will build public trust and that will get us where we need to be.

The second answer is there's no choice but to make sure that these efforts are in synch, at some point intersect. And the reason for that is, one, we've proven it can work. Two, we can't afford as a nation to do it any other way. And three, it's the right thing -- that's been said before.

I would very much disagree with the comment made after the last panel that we have to tempt people that every sector is in it only for what it can get out of it. And, in fact, everyone we've approached since starting this effort has pretty much uniformly -- almost without exclusion said, of course it's the right thing to do.

Yes, we all have specific interests and

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

specific needs that we need to meet for our sector. But there really has not been pushback.

But again, we've done very carefully, in a very measured way and a very transparent way. And I think we're slowly building trust, which is why the discussion about privacy today was far more broad -- sort of not just thoughtful but imaginative than we've had in the past. In the past, we've very much retreated to -- Kristen was smiling. Oh, we just won't -- we won't let a PHI transfer. And that's not feasible. We all know that. We don't want to admit it, but we've all gotten to the point in this conversation now where we can admit and think about how to do it.

Because, in fact, very early on we were going to have to do it. And we can't just rest, because we are trying to build a national resource, both for safety beyond FDA, and for comparative effectiveness. We can't rest on, well, is the FDA doing our business, we don't have to worry about it. We have to solve the problem more broadly. Although, as FDA focusing on the fact that we have a statutory mandate to protect the public

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and we are going to very carefully continue to do that.

That's why up until this point in time, we've been -- or at least I've been. I'm looking at Jen, she's been less so. I've been very reluctant to engage in this discussion, because there was, I think, a real concern that we might fall victim to unrealistic expectations and goals that we couldn't meet. But we've got a toe hold in now, we've made some progress, and we can start expanding our discussion as we continue very methodically to build Sentinel.

So, I think the answer is the challenges for this panel are the same as for the previous panel. Very much as you expand what FDA is doing beyond what FDA -- just FDA, the governance issues become far more complicated -- Mark, you asked my question, but slightly differently. It's not just -- is it in industry studies and FDA study, but where do -- how does it get -- who pays for it, but how does it get queued up? Does it get queued up as an FDA study, it means it goes first? And so forth.

So, extremely complicated, but solvable.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

We've proven that these -- it's solvable. OMOP has proven you get enough thoughtful people together, really you can accomplish a lot in a very short period of time. And I would remind those that were here from beginning that we've been doing this for approximately 20 months and we're essentially ahead of schedule. And in the federal government that's extremely unusual. (Laughter)

I want to echo one other point Paul just breezed through, but it's really crucial. Which is training. If we as a nation don't think about how to train the Pharmaco-Epi folks, the stats folks, and others that -- to do this work and we don't clone Patrick, we're not going to have people to do the work, even if we can figure out all the other governance issues. So that's -- that keeps getting pushed aside, but someone's going to have to tackle that. I'm not sure the FDA can, but someone's going to have to or we simply are never going to get the industrial strength system that Rich described, and we're going to end up like Lucy eating all the chocolate.

So, I think in summary I'm amazed how far

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we've come, I'm amazed at the amount of trust that we've been able to build, I'm amazed at the amount of cooperation we've gotten that far exceeds the very modest amount of contract dollars that have flowed from the FDA. And so I -- I'm very optimistic that a year from now, much -- when we have yet another meeting -- much of what -- or many of the points we struggled with today will seem not so daunting. And -- but of course we'll be facing new ones.

Thank you. (Applause)

DR. McCLELLAN: It's always a good sign at the end of the day when Rachel is not holding her head in her hands and moaning, so we'll take that as some measure of success.

Opening -- I'd like to open this discussion up again to those of you who are here. So, if you have any comments or questions, please head for the microphones as before.

Just a comment for -- or question from me to start off. One of the things that Carolyn's presentation highlighted is that there are a number of

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

networks out there that are working in both of the areas that we've focused on today, namely post-market active surveillance, but also comparative effectiveness research of various types, but as well quality measurement and so forth. And they're typically doing it with FDA or with AHRQ or with the new initiative from ONC. Could you all both -- and I don't mean to put you on the spot here, but kind of comment on how that's going. Or maybe if there are some of you here from some of these networks, I-3, Healthcorps , so forth -- I'm putting you on the spot. You might have some comments as well.

Are -- is it your sense that we're getting -- or we're taking advantage of the potential complementarities here? You know, at a basic level some of the -- as Carolyn pointed out, the data infrastructure needs are similar, perhaps some of the common definitions which everyone has stressed is absolutely critical and difficult to get right. It seems like it'd be nice if we could get that right once for multiple types of applications, but maybe that's not

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

feasible.

Any thoughts on how this kind of coordination is occurring now?

DR. BEHRMAN: I think -- going to start, which is that, in part, that is actually the concern, that there are many efforts and if we don't do a very careful job inventorying them and making sure that we learn from them, that there will be the kind of duplication that we're trying to avoid. And I think we at the FDA find ourselves, again, in the unusual position of being a little ahead of the curve.

So what we hook on to -- will ultimately depend on what's available. But if it's multiple different efforts that are disparate, it'll be much harder to achieve.

DR. CLANCY: Well, I guess I should say, not entirely irreverently, that actually we work incredibly well with FDA. We hire some of their great folks, and they hire some of our, and we know it all -- one of them whom is actually detailed back to work with us for a while. So it all works out just splendidly.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

I would say -- at an informal level we do a great job doing that. Which is a little bit different than doing it at a sort of strategic level. I don't mean that everything has to be, you know, this initiative in capital letters. But I do think there's a quasi-urgent need to develop better vocabulary. So, it's very, very clear that when the people who -- you know, whose brains are totally wrapped into adverse event surveillance say X, that's actually pretty much the same thing as what the CER folks are calling Y and what the quality folks might call something else.

I mean, I think we're missing that opportunity. And certainly, as these efforts mature, there will be more and more opportunities to do that.

DR. McCLELLAN: Jonathan, then Mark.

JONATHAN: Actually, I have just two questions for Carolyn and Paul. So, on the Paul -- I noticed, I thought, a spread between your positions just a definitional thing around -- Paul made a distinction between comparative effectiveness -- which if I heard you correctly, said it really speaks to population level

Comment [M.C .1]: Jonathan Hare?

yes

issues. And then personalized medicine where it's about the individual.

And what I heard Carolyn say is, you know, hey, we're not done until we actually feed it back directly to a care delivery environment or to the patient themselves.

So in that sense, I mean, I don't believe -- comparative effect is my view. If we do it right, is really about personalized decision support. Not about enabling bureaucrats to change reimbursement levels for entire populations.

DR. STANG: I guess at that level, we're probably saying the same thing. I guess, what I was trying to strike the balance for was someone who's making a decision about one product versus another at a population level versus what I understand to be the concept of tailoring treatment for an individual based on their individual characteristics.

An extreme example of that actually happens to be something our company is doing over in Europe, which is kind of a pay for performance kind of approach

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

where you only are reimbursed for a product in patients in which it works. So, it's a kind of a no-risk for the patient and the payer. But it's the same idea because they've got projective models as to who will benefit and who will not.

MR. HARE: I think it's an important distinction, because we -- a while back we took a tour through Congress meeting all the leadership in the different committees. And on the, you know, dare we say the Republican side, people who believe fervently in capitalism were -- what we heard is really afraid and against comparative effectiveness research. It's like, you know, I thought you believed in capitalism, which means price transparency incentives. I don't even know how you do it without transparency to costs and benefits.

But I think where it came down was, they perceived it as a tool for bureaucrats to set reimbursement at population level. If you said, no, no, no, this is for personalized -- this is in support to get the right treatments to the right people. Then they

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

could conceptually get there. But it wasn't being talked that way. so, I think it's important to clarify what we're talking about.

DR. McCLELLAN: I'm a scientist, not a bureaucrat or a payer. So --

MR. HARE: Yeah. No, I think we're on the same page. I just think, you know, the terms matter and how they're interpreted matter. And there's a lot of polarization, which I think is really unnecessary.

The other question is for Carolyn. You spoke at a -- you were supposed to be in Berkeley for this Right Care Summit? Except you got stuck in New Orleans. But you made a very inspiring speech, which we all appreciated.

But you mentioned that -- she did -- so always good to have true believers. But you mentioned that to date after all this -- your characterization of the efforts to share information, do comparative effectiveness, and all these other things was glacial. That the progress is absolutely glacial and we need to try new approaches.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

So I'm wondering if -- I've been seeing recently more innovation-centric model. And people kind of reopening things up. And I'm wondering what your -- you still think it's glacial or do you have more hope for the pace?

DR. CLANCY: So, I think what I said was glacial was actually closing the gap between best possible care and that which is routinely provided.

Now, I do think there's a unique opportunity, and you're framing it as personalized decision support was, I think, very, very clear. So thank you for that. I'll be quoting you a lot.

You know, ultimately we could be measuring quality in terms of informed decision making rather than saying, you know, this is the right thing, did you get the right thing or not. But the point is, you know, if you look at the metrics -- particularly for chronic illnesses, I don't mean ordering the test. I mean actually intermediate outcomes, you know, 60 percent's kind of a high watermark. These are for insured patients, which makes you wonder what are we missing

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

here. There's something wrong that we're not doing better than that. That's what I was saying I thought was glacial. But I very much appreciated your comments.

DR. McCLELLAN: Thanks. Marcus? You going to be okay here?

DR. WILSON: The -- you ask for comments for sort of our perception around the coordination between the efforts around HIT, around safety, and around comparative effectiveness. And I think --

DR. McCLELLAN: Oh, and quality measurement.

DR. WILSON: -- quality measurement, pay for performance, all those things. Yeah, they're -- I think it's a couple of things really important.

One is, I think that there's a lot of the -- a lot of the funding opportunities are now starting to come out. And if I throw AHRQ now into that mix in terms of the types funding opportunities that come out in the prospect, grants, et cetera, I think there is a common theme around building an infrastructure for evidence development of all types.

And so I think whether or not it's purposeful

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

and coordinated or just coincidental, I'm not behind the scenes. You'll have to tell me that part. But it does seem that there's a nice, solid theme building on that we need an infrastructure with. And whether we're attempting to leverage the same infrastructure or not, I think that's the intent part that only you can answer.

Those of us that are on the other side of that, that are building that infrastructure pieces within our own environment and then working to collaborate with you, we are doing that. That is what we have in mind on our side to leverage the same infrastructure that we're creating and to work on both safety and on comparative effectiveness. And those are really key, because it's all very similar methods to all of them. Different end points, but similar methods.

From the HIT perspective, we help set up a very strong interest from a parent company with a null point for (inaudible) Health Information Technology, and we do work hand-in-hand with that group. Because I think HIT is a really important part -- in part for the research. I think it's going to help open up the pipe

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

to connect to some of the data. But we have to realize that one of the most important things that we're going to do in terms of generating the evidence is being able to act on the evidence once we're done. And if we consider that there's -- I think there are numbers -- 700,000 plus new citations on Medline every year, we have to realize that just generating more evidence is not really going to help us improve the quality of health care.

So, Health Information Technology is going to give us the pipes, again, to go back out with the information, but a critical aspect even of that is to make sure that we're building decision support. Because again, we can just continue to open up more and more data to the providers and to the patients. And they're not going to be able to use that information effectively.

Especially when you come to individualized medicine. So, yeah, from our perspective there's a very strong theme on that and we appreciate the new opportunities as they're coming across.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. McCLELLAN: Building decision support, I hear that. And kind of the use end of all these types of related evidence. But I didn't really hear any concerns or suggestions around building the infrastructure itself in a way that's -- that could be better coordinated. Is it -- it's headed in the right direction now?

DR. STANG: Well I think that -- I think the opportunities are there. I think in some cases -- and we're looking to try to get involved with them. What I don't -- I think the FDA, it seems -- from our perspective it seems the FDA is trying to stay focused on active safety surveillance. And I think that's part of it.

I think AHRQ is focused on comparative effectiveness. It would be good -- in my opinion, to really try to coordinate even that infrastructure build because what we're going to wind up getting, I think -- I worry a sort of different mix of players on both sides of that. So, to some extent, if we can sort of overlay those a little bit more deliberately, that may actually

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

be -- we may actually wind up with a more -- if the desire on both parts is to build a permanent infrastructure, then trying to overlay them may be a stronger model to some extent.

DR. CLANCY: So, first let me say that all federal activity is strategic and purposeful by definition. (Laughter)

So, with that as a starting point, I think that you've made some very good points. I mean, certainly there has been a fair amount of collaboration between AHRQ and FDA, but as we get into this area, I think there could be even more. Janet and I have had some recent conversations about this, so spiritually we're with you.

I wanted to actually -- I will say two things, though. One is, on one level you don't want this too tightly bound, right? Because you want some innovation, you want people trying some stuff. because I don't think anyone would have thought that you could do Dartnet, the Colorado one with the small practices, if we hadn't actually specifically requested it and put

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

out an RFP. And it worked really -- I mean, it looks very, very promising. So that's one issue.

I think your other point -- I'm going to restate as saying that we need to keep our eyes on these strategic goals all the time. And remind folks who are way down in the weeds of building these efforts. Because one thing that I've noticed happening in quality a bit is, we start to think that once we've got the report cards, that's it. Care gets better. And I wish it was that easy. But what -- you know, we have a long way to go. That's the glacial part, to the earlier question.

DR. McCLELLAN: Marcus, I just want to ask one question. And it's -- I'm not intending to put you on the spot, but let's say that you can implement exactly the vision that you just articulated. But you're implementing it as a health care payer organization. Is there anything that prevents you given that business structure of sharing that transparently across the entire health care system -- in other words, are you in a situation where it becomes a competitive

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

advantage and puts you at -- again, I'm not trying to trip you up, but I'm just trying to -- there are conflicts within all of the things that we're doing. And this is potentially one.

DR. WILSON: Sure. I think, from our perspective, we're a very transparent organization. In fact, we've got an article that's coming out right now on all -- we did a lot of signal validation work over the last 18 months as we're looking to field -- as we just fielded our safety Sentinel system within Wellpoint.

The -- all of those we're going to make public domain. Very much like the same spirit that OMOP is being -- is making all their work transparent, so are we. So we're looking to advance the field and try to get everyone on the same level playing field.

And so in terms of -- it depends on what you mean by transparency. I -- for us, we really haven't filed patents, we haven't looked to hold most of our things that are -- that we're -- the work we're doing. We're being very public with that work, and very

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

collaborative. As collaborative as we possibly can be as an organization to try to make sure we're moving it forward.

And I think to some extent, for us it's sort of in the mission of what we are as a health care organization is to try to improve quality of health care. I think we all benefit from it, and I think that the health plans that are part of our parent company really want us to do that as well.

MR. GREBERMAN: Mel Greberman, Public Health Resources. I'll try to make it not too loud.

My question will be for Dr. Clancy. First, I want to make a brief comment.

One, I very much agree with your statement about how important, how great it is of the FDA and AHRQ are working together in many areas. I've retired from the Public Health Service and FDA in 2001, and so I must state that this has really been a long relationship. I was very fortunate to start working for Mike Fitzmorris in 1980s and really that -- working together in collaboration with Mike and many other organizations,

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

really got this whole thing a long way in terms of the informatic standards areas. So I think it's great that it's continued and even growing.

So, that's my comment.

The question is, similar to one I asked of Janet Woodcock earlier. To what extent and in what way AHRQ working with the biomedical informatics grid, which is the consortium that's grown out of the CA big project sponsored by NIH and is working in coordination with the health and women study, which looks to have like ultimately 1 million women as a study population. And clearly, I think that there are many issues that Dr. Clancy mentioned that very much are relevant and vice versa to what the -- is going to be happening now, the big consortium.

So I was just wondering, how closely are they -- are working together and in what way.

DR. CLANCY: First, thank you for the compliment.

Second, we are very much aware of their potential. I'm not sure we've entirely identified all

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the points of synergy yet, but it's very much in our minds. And I'd have to say, the past year with the ERA funding has been really remarkable for really elevating lots of informal relationships between AHRQ and NIH to a much higher level. But NCI has been a longstanding collaborator.

MR. GREBERBIN: Great, thank you.

DR. McCLELLAN: Diana?

DR. ZUCKERMAN: I'm Diana Zuckerman from the National Research Center for Women and Families.

Thank you. This is a great panel and a great day. I was been very interested in thinking through or trying to think through, as other people have, what is really the difference between comparative effectiveness research and the Sentinel project in the sense of, it's the same data sets, potentially. They can be analyzed in these different ways at the same time. You have two different agencies, it's always hard to get those two -- you know, any two agencies together.

But is there really a distinct difference -- is there a reason to analyze these separately versus

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

together but having two different agencies translate the findings in a different way.

DR. McCLELLAN: If I could just make a comment, too -- and I do want you all -- it's a good question and the answer is, back early on -- and you may remember when FDA AA was being enacted. And when this post-market effort was being set up, there was a lot of concern that safety issues would get separated from effectiveness issues. Why does everybody at the FDA keep saying you've got to -- you know, there's no such thing as a completely safe medical product. You've got to always look at risks and benefits together, does the same thing go along on the analytic side.

DR. CLANCY: Yes. So, I think the short definition -- first of all, for those over here don't know of Diana Zuckerman's work, you should. She does fantastic work. So, just needed to say that.

You know, our shorthand would be to say that everything we do in CER is about looking about benefits and harms. And adverse event surveillance is more exclusively focused on harms. Although, you still have

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

lots and lots of situations where you're trying to manage a risk benefit sort of balance, if you will.

So, for example, a report comes out from a case control study that suggests that people on X, Y, Z are at increased risk for something. Well, what do you do with that. I mean, this is the kind of stuff that FDA struggles with all the time.

I think the other place we differ in terms of statutory mandate, which Rachel started to get into before. And the FDA has a statutory mandate to act -- we actually do not. In fact, we may not make standards and so forth. So, to that extent, I think our sort of perspectives are complimentary. But the methodological underpinnings in terms of differentiating signal from noise, I think, are more unifying than not.

I hope that helps.

DR. STANG: Can I just add a little bit -- I think the other thing that I distinguish here is, the safety questions usually -- you pretty much rely on existing data. Pretty much.

Effectiveness data, you can start being very

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

clever -- and I'm looking at Rich because you've got the HMO research network, and you can certainly imagine that if you believe that there's clinical equipoise between two different products, if our EHR system is going to be as great as we think it is, it's entirely possible to understand that at some point in time, a patient that comes in that meets a certain profile, little window pops up, asks them to consent to be randomized to one of those two treatments. And the data collection form which now is this humungous thing becomes the electronic health record. And it gets back to the whole idea of a learning organization, it engages people in research, and it's much more on the effectiveness side -- I'm sure there would obviously be some safety issues.

But that's the kind of thinking that I believe we need to think outside of just collecting data and analyzing data that already exists. It's kind of pre-imposed. It's what's there and what's going to make it better. And I think that's the real strength here. And we haven't really talked much about that today.

DR. BEHRMAN: The only thing I'd add is, when

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

we started, we tried very hard to introduce the concept of performance. Echoing exactly what you and Mark have said, that there is -- you cannot separate safety from effectiveness.

But that wasn't the national dialogue going on and so, it wasn't the right time for that. I think the power of this effort is that we are building a slightly more informed national dialogue, and in time we may be able to talk a little bit more -- with a little more precision about really what safety means. But at the moment, that is as the buzz word, and in fact the tool that we are developing first is a specific tool to answer a different kind of question about adverse events than currently we have had.

DR. ZUCKERMAN: But -- I'm sorry, but wouldn't you be looking at outcomes. So, did the patient live or die. So, yes you want to know if they died from liver disease when they were being treated for pneumonia.

But wouldn't you -- I mean, wouldn't that be part of the outcome, not just the adverse events. But

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

the outcome, success or failure, live or die, get better or not.

DR. BEHRMAN: Well, there are two answers to that. The first is that obviously, we use this as a tool, as Judy and Chris mentioned, one more tool, one more source of information to factor into our decisions.

But -- and I'm not a methodologist, but the others in the room know better than I do that asking the kind of question I think you're alluding to, which is not only did the patient die from liver failure but did they do worse or better on that therapy than another one is a far more complicated question involving different methodologies and different types of queries than the more initially planning.

Again, just -- the way to -- the fastest way to harm this effort is to get too ambitious too quickly. So, we have to, what is the expression, crawl before we walk and so forth. So, we're starting with this.

DR. ZUCKERMAN: Thank you.

DR. McCLELLAN: Last two questions to finish up.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. WEINER: So, I'm Mark Weiner from Penn. Carolyn, you spoke to incentivizing the data collection process. And one of the opportunities for incentivizing that process is through improving the billing data capture in a way that supports this kind of work.

So, right now the way ICD-9 and even ICD-10 and 11 as far as I know are constructed, the advantages of ICD-10 and 11 over ICD-9 seem to be a precision of the term without necessarily reflecting the integrative thought process of the clinician.

So, the difference between a -- I have a leg swelling, so I can put leg swelling or I could put DVT; or I could put rule out DVT; or I could put low likelihood of DVT, high likelihood of DVT, or following up with DVT. And right now, when I bill, the terms that I choose don't capture those nuances. And I think that kind of inflection could be especially valuable for the kinds of processes we're opening.

But obviously, I personally -- we can't influence how billing -- the billing rules, and how they are captured and translated. Or do we have that power.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

DR. CLANCY: That would be a topic for another meeting. So, I think Mark should think very seriously about that.

I think one of the issues is not related to which ICD system, but is actually about the spectrum of disease that practitioners see within their population. Right? I mean, by definition, specialists tend to see a different crowd than primary care clinicians. And, you know, there's obviously kind of a huge spectrum with people on multiple points in between.

I looked at Paul's slide on the dementia study, which I thought was really cool. And what I realized is, if you could engage clinicians who had a vested interest in being real clear about what's the prevalence of dementia so that they could figure out what to do and what's working and what's not, you're still going to need the judgment of an expert clinician in terms of some of this data entry.

In theory, a lot of that will get much easier with advances in health IT. But I don't see that need going away real, real soon.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

And I don't know about the billing enterprise.

DR. McCLELLAN: Well, I would just -- before we get to the last question, remember that billing systems and reimbursement systems are evolving things as well. Just like these data infrastructures, I would bet, Paul, that the data reporting that goes on for J and J's product in Europe that is reimbursed based on diagnosis and outcomes has pretty accurate information about diagnosis and outcomes that would be suitable for some of the kinds of outcome studies that we've talked about here.

So, again, I think it goes to the synergies of -- the potential synergies of all of these efforts.

Next question.

DR. HILL: Thanks, Mark. Jeffrey Hill from the American Medical Group Association, more specifically the Anceta Collaborative Data Warehouse. As many of you know, we've been trying to drive the data-driven quality improvement for quite a few years, and we're finally getting there.

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

But it seems that we focused in this room today about the extension of the Sentinel initiative to comparative effective research. And quality improvement has been mentioned a couple of times in that same context, which it should.

And of course, the IOM had considered the delivery system itself as part of that CER spectrum. But a lot of what our interest is, as I think -- as Fran Cunningham said earlier today, it's not just what drug or drugs were used but how those drugs were used.

And of course, we're focused on what are those processes of care that get the best outcomes. Even for a specific type of drug or class of drug.

So, I'm wondering as we look at enhancing the Sentinel network to expand it to a number of different initiatives such as CER and the like. How do we feed into that equation process measures and process improvement so that we don't lose that important piece of how we improve care.

DR. CLANCY: So the quick comment I would make is just that if you were to read either the House

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

or Senate bill right now, you would see that there's a lot of interest in a science of improvement.

But I would also say that in -- for some of the areas you've just mentioned, we almost need to build a basic vocabulary. I mean, at the end of the day, you know what a pill is. We don't know if someone's taking it, but by and large we sort of have some standards around what the intervention is.

When you're talking about the interaction between patients, clinicians, health systems, and so forth, it gets very, very tricky. Which doesn't mean that we don't desperately need to learn about it; we do. But I think it's an order of magnitude more difficult.

But I think that's another payoff here.

DR. BEHRMAN: Just to remind everyone, there is no Sentinel network yet to enhance. Not to --

(Laughter)

So, I think what we can do is develop a to-do list -- and that's why, Mark, your question about are we doing enough to make it one network may be a little premature. We just have to make sure we keep it in mind

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

as we -- so we don't back ourselves into a corner and not do something we ought to have done.

DR. McCLELLAN: I'd like to thank the panel. We don't have a Sentinel network yet, but there is clearly plenty of interest in where it's headed.

Thank you all very much for an outstanding discussion. (Applause)

Now, we are just about but not quite done. I want to remind you that this is part of an ongoing process to try to make sure that Sentinel activities are transparent and that we are raising these not only short term implementation issues but broader analytic issues and strategic issues about where the program is going.

And I'd like to particularly thank the people who are involved in bringing this meeting together today. All of our speakers, who were terrific, as well as the staff at Brookings and FDA, who cooperated in planning this event. That includes Rachel, who you just heard from, Melissa Robb, Judy Racoosin, and Mitra Rocca. From Brookings: Josh Pfeifer, Megan Carey, Nadia Nguyen, who did a great job of keeping people pretty

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

much on schedule, Erin Weireter, Marisa Morrison, Beth Rafferty, Brynn Barnett, and Sally Cluchey, and Josh Benner, and Larry Kocot, all of whom were just terrific.

So, I'd like to thank all of our organizers for this event. (Applause)

DR. McCLELLAN: And two other groups who I know are all very busy -- we had a lot of people here from the FDA, and had a lot of very useful interaction as a result. So I'd like to take a moment to thank all of you for taking time out from your very busy schedules these days to make it to this meeting. And, most importantly, I want to thank all of you who participated. This has great back and forth dialogue, as you can see. There has been some very important progress made on Sentinel over the past year, but many significant, important challenges and issues ahead. This has been a great discussion to help us think further about those.

And with that in mind, I hope all of you will stay engaged in this processes in offering ideas and feedback just as was the case today. There will be a

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

transcript and slides available from today's meeting on the Engelberg Center website at brookings.edu.

Actually, all of the relevant websites are up there on the slide right now. Some of you were asking about this earlier.

So, there definitely would be a place to go to look for further information related to the Sentinel initiative. And it provides some feedback on how to make sure it's implemented as effectively as possible.

But again, thank you all for making today possible. It's been a real privilege working with you. Thank you very much, and have a good evening.

\* \* \* \* \*

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190

## CERTIFICATE OF NOTARY PUBLIC

I, Carleton J. Anderson, III do hereby certify that the forgoing electronic file when originally transmitted was reduced to text at my direction; that said transcript is a true record of the proceedings therein referenced; that I am neither counsel for, related to, nor employed by any of the parties to the action in which these proceedings were taken; and, furthermore, that I am neither a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

/s/Carleton J. Anderson, III

Notary Public in and for the Commonwealth of Virginia

Commission No. 351998

Expires: November 30, 2012

ANDERSON COURT REPORTING  
706 Duke Street, Suite 100  
Alexandria, VA 22314  
Phone (703) 519-7180 Fax (703) 519-7190