# IMPLEMENTATION OF RISK MINIMIZATION ACTION PLANS TO SUPPORT QUALITY USE OF PHARMACEUTICALS; OPPORTUNITIES AND CHALLENGES: A PUBLIC WORKSHOP

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# T A B L E  O F  C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

DR. TRONTELL: Good morning. Welcome back to day two of our conference on risk minimization action plans. I want to thank all the participants from yesterday for the very interesting presentations and very fruitful discussions that took place. I'm looking forward as are you I'm sure to more of those happening today.

I want to have just a minute though to make special thanks to the joint team, FDA and AHRQ, who planned this conference, many individuals who I won't list separately. However, I do also want to acknowledge the special logistical challenges that we've encountered here at ARHQ and make special thanks to Jean Slutsky for supporting the conference and its associated costs, Amy Lindinhau who may have been the one who let you in the gate this morning when we found out we ran out of tickets, Parivash Nourjah, Beatrice Canyas (phonetic), Martin Ehrlichman, Shelley Anderson, Debbie Voight (phonetic),

Jackie Carrie, Latrice Stewart, and many others, including our Security staff.

To that end, I do want to note some of you may

have inadvertently retained your pass code from yesterday. We ask you to look at those. I actually have a list of about six individuals. If you would please be sure –- Lilly Chan, Elizabeth LaGow, Craig Metz, Ralph Preiss, Emily Yow, and Petinotti (phonetic) and George Hemsworth –- to return those to us.

Next what I would like to do is attempt to introduce a person who probably needs no introductions. Hugh Tilson, distinguished professor in epidemiology who is a good friend to FDA and to AHRQ and is notable as chair of the National Steering Committee for the Centers for Education and Research on Therapeutics. Hugh.

DR. TILSON: Thank you. Thank you for that brief introduction. I would prefer it be briefer, but there you go. Thanks, Anne, and thanks all for being here. And thank you in the home listening audience over there at FDA, long suffering and long listening. But the good news is that you have a chance to listen to me slower

because you can record this and play it back at a reasonable speed.  The people here are stuck listening to me at this speed.

I am Hugh Tilson. And as you know, I'm chair of the National Steering Committee for the Centers for Education, Research on Therapeutics. It was wonderful yesterday to hear CERTS mentioned again and again and again. And you'll hear it mentioned again and again today because it is the partner agency under AHRQ's partnership with FDA to deliver on the public health side of all of this spectrum. That is if the RiskMAPs are looking at severe and unacceptable but rare events, CERTS are helping to look at the overall impact of therapeutics on public health with and for the Food and Drug Administration. Here's my conflict of interest statement. See Brian Strom, his conflict of interest statement.

I have the privilege of summarizing day one. Now day one was extraordinary and full and long and full of all kinds of wonderful comments and ideas. And so I would like to summarize by quoting a few of the definitions that I heard. There were some quotable

moments that I wanted to tell you about, a quote, but a promise that this is just my selective listening. If you don't like the way I quoted you, you have full rebuttal opportunities. Just not now. And then touch on a few cross-cutting issues and lay out the challenges for today and particularly for the panel that ends the day. If you're planning to leave early, I wouldn't blame you, but I'm chairing the last panel, and we'll have all the panel chairs together at the end taking a look at what they have heard and what it might mean for the future of this field, particularly the action agenda.

First, let me remind you of the exhortation from Jean Slutsky, and that is we're here to listen to each other. So that's what I did, including doing some spying last night at the restaurant, those of you who were sitting at the other tables and talking about today. Watch for some of the things you said on these slides too.

Before I start, let me just say a word about my

dear and departed friend, John Eisenberg, for whom this building was named. He would be thrilled with yesterday because we actually did what the program was supposed to do.

You may have not listened to Paul Seligman. For those over at the agency, that’s not unusual I understand.

But Paul was his usual wonderful, wise self, and he said that “our real purpose here is to get to know one another, get to know each other’s agendas and concerns, make some new partners and new friends, and then get on with it.” And we certainly have done the first three and maybe we’ll do the fourth today.

So here’s some definitions I heard.

I heard Jean Slutsky say “AHRQ is an agency which addresses very important issues with very minute budgets.”

Rockville was defined as a “highly volatile area requiring tight security.”

FDA was called –- thank you, Paul, for this –- a public health institution. That, for those of you who don’t know, is new. That was actually promulgated in the FDA Modernization Act of 1997. Before that, public health was not in the Food and Drug Administration’s mission.

“FDA, I won’t use the word reform when I discuss it,” one of you said. FDA was described as an “honest

broker to bring together the varying interest, particularly in this field.” And finally FDA was

recognized, “however errant its actions, as motivated by the best of intentions.”

We heard from Sidney Kahn that in the U.K., they pay GP’s 150 grand, and that’s in pounds.

We heard distribution centers described as “part of the problem –- er, um, program. You’ll remember my talk, won’t you.”

And of course, we heard Brian Strom’s conflict of interest slide described as an eye test. Thank you, Brian, for that. Brian actually used the term Holy Grail and said that was really the –- was personalized medicine. That’s where we need to go. And RiskMAPs are a step toward the Holy Grail.

RiskMAPs were also defined as “most of them are there for a reason, and they’re all different,” said someone from the Food and Drug Administration, which is quite true, thanks, Sandy, for that.

“RiskMAPs preserve access to drugs which otherwise would be lost.” Isn’t that a little pearl on

yesterday? Which otherwise would be lost.

"RiskMAPs compromise continuity of care and delay access to medicines," say 82 percent of hospital pharmacists.

"RiskMAPs are the rare and happy situation. That is where we could actually do things proactively." Thanks for that, Dr. Metz.

"The goal of RiskMAPs, every patient will demonstrate a basic understanding of the drugs they are about to take." Of course, wouldn't that be wonderful if that was the goal of medicine as well?

And REMS. REMS were described as "Congress catching up on what FDA was already trying to do."

Physicians, at least some, are called "graduates of the Jekyll and Frankenstein School of Medicine."

"Physicians were called risk adverse and adverse –- Joe, I hope you're taking notes and taking this back to the House of Delegates of the MA which is meeting as we're speaking here –- risk adverse and adverse to

cumbersome procedures.”

Primary care physicians, “a ready to collapse system.”

Evidence-based medicine, “it takes time, which is precisely what I don’t have.”

Warning fatigue. How many are too many warnings? Can we stop those silly seatbelt demonstration on airplanes?

And TOUCH, what you can’t do with the slides from the TOUCH program.

“Consumers are not an easy crowd to keep safe,” said the Consumer’s Union.

“And bikers without helmets keep the organ banks in business.”

Here was a touching moment when one of our most articulate patient advocate said “I’m the patient. I’m at the bottom of the food chain.” He actually said it. And while he said it with a smile, we better listen. He then proceeded to tell us what was going to be in this week’s

New England Journal of Medicine.

Healthcare delivery system. Ann called it "fractionated and sometimes fractious" –- I love that. That's a great tone of phrase –- "and drugs. As with anything else, there are some benefits and some risks."

And of course, our risk management dilemma is to keep in balance always this notion of benefits and not just the focus on the harms.

Well, here was some quotable moments after all those definitions:

"RiskMAPs are not new. Clozapine, the no-blood, no-drug RiskMAP, was 1990." And then in the next breath, "RiskMAPs are new with PDUFA 3 in 2002 and everything that's come since then."

A challenge for the evaluation panel, this is very humbling that we would at this stage still be in the position of describing the only real evaluation program as there is some evidence that the program is effective. We have work to do there, and Ann tried to tell us –- going

to walk us through that.

"Today the plural of anecdote is not data," thanks, Brian for reminding of that. "And the question is the great guru says what is the answer, and the answer is my son or daughter, what is the question." That's Brian Strom's favorite. Mine too. And the question is, said Brian, "how, despite this disarray in healthcare, can we improve patient care and this case in therapeutics. The problem is we focused in the past on the tyranny of the average." Well, nice. I don't know what it means, but a great quote.

Here are some directions for us:

"You do wish to restrict physician behavior that is irrational." That's true.

"RiskMAPs are useful in protection of drugs and not just patients."

There's something in this for the pharmaceutical industry as well. "There's no silver bullet here." Therefore there are few people who even remember the Lone

Ranger.

“The patient already compromised should not be burdened with confusing enrollment processes. The doctors, I asked, could see the need for control but found the system onerous. I’m here to learn. After all, I have to report back to all those doctors I’ve been talking to.”

The doctor said, “RiskMAPs, not on my watch. I don’t want to get sued.”

“Would a patient say a checklist is degrading and insulting to my professionalism? As a consumer, it makes me grumpy when doctors say that.”

“How can we make it easier for physicians to do the right thing? For that matter, make it harder for them to do the wrong thing.”

“You don’t just do one approach to RiskMAPs. Some physicians actually want a little card in the pocket of their white coats.”

“You really have a hard time believing everything that pops up in a pop-up window, in case you

think we have that technology of warnings and signals of risks and edits, right? Let's use carrots and not just steaks."

"Our current fragmented approach is not going to support the coming reality." Interesting.

"Programmers need to be paid too incidentally." I noticed several others of you representing your profession saying so do I.

"It's not just who is the subject of a RiskMAP. It's who is left out."

"And if the patient doesn't get the RiskMAP product at all, you still have a problem."

"What we really need are full proof systems," said on pundit. "Wouldn't it be nice if we all had E-prescribing?" Well, maybe.

"Help me to do what I am –- oh, help me to do what I'm doing anyway by building RiskMAPs into the workflow. I'm trying to do this anyway."

"There are processes we can adapt and adopt from

the disease management safety management world."

"Let's take RiskMAPs and put them into existing systems." Very wise person.

And then in his keynote talk, Brian Strom actually as always put my thinking on its head. That's why I don't have any hair left because I listen to him a lot. "Perhaps RiskMAPs could be the driving force behind health system reform." That's actually a paraphrase of some very wise management gurus who say if you want to solve a little problem, make it bigger, and then solve the big problem and the little one will solve itself.

So where do I take us today? Well, here are the cross-cutting issues I heard on the basis of these and the other notes I was taking. It was a wonderful, wonderful and constructive day. First, I didn't hear anybody say we don't agree on the objectives, although we could polish them and refine them. But not disagreement about what we're trying to do here. But we're not yet in agreement on the methods.

For example, regarding standardization, each RiskMAP is unique because each risk situation is unique. Otherwise we wouldn’t be there. This is actually a system to address unique situations. But the systems in which they asserted require standard procedures. Structured strain. And this afternoon, let’s talk more about that.

Transparency, another strain. Adoption requires acceptance, and acceptance requires understanding. But the sector also requires intellectual property protection. And it has yet to develop effective communication to assure understanding for adoption. Or maybe it’s even worse than that. They do understand what we’re telling them, and they don’t agree.

Empowerment. Management requires control, of course, but professionalism requires flexibility. Regulation is central, implementation is local. Structured strain. Pharmacists saying come to us first, industry saying come to us first. Resource is likewise. Specialized processes increase costs at the very time that

we are deploring the costs of healthcare. Structured strain.

And then the evidence. Risk management is an intervention, and interventions are therapy too. And they require the same ethics –- we haven't really talked much about is it really ethical to be conducting this grand social experiment. Do we have the informed consent of the people on whom we are experimenting with this intervention? How would we get it, and proofs under the challenge for the Evaluation Committee.

So the challenge for the final panel after we hear from today will be the fifth of Paul Seligman's challenges, namely what are the action –- what do we need to do? What are you going to do differently when you go home? We'll come back to that in the last panel.

And the challenges for all of us today then are to go back to the overall challenge of this workshop, which I love, promote interaction, promote information sharing, and listen to your partners, improve our

understanding of the healthcare delivery system processes into which RiskMAPs need to be put so that they may be effective. And then we'll be able to develop actual steps. Great first day. Let's see how we do in the second.

DR. TRONTELL: Thank you, Hugh. I don't envy anyone who has to follow Hugh at the podium. We're going to hear next from an industry panel. After that, we'll have the open public hearing. Any speakers who have slides for that, please see Lee Lemley so we can load them onto the laptop at the break.

Let me introduce Gerald DalPan, who's the director of the FDA's Office of Surveillance and Epidemiology. He's a neurologist and trained in many fine institutions, including his public health training from Johns Hopkins. Gerald.

DR. DALPAN: Okay. Thank you, and welcome back to a second day of this workshop. Yesterday we heard from a number of stakeholder groups, the patient advocacy and

consumer groups, provider and payers. We also heard from pharmacists and pharmacy systems and distributors. And today we're going to continue that, and we're going to hear from another group. We're going to look at the industry perspective. We have three representatives of the pharmaceutical industry. And each of their companies has a product which is the subject of a risk minimization action plan. And in bringing them here today, we asked them to consider a few things to focus on in their discussion, what tools they're using in their plans, and how they chose them, how they evaluate their plans, and what challenges they've had in developing the plan, implementing it, and evaluating it.

Our first speaker today is Dr. Carmen Bozic from Biogen Idec, and she'll be talking about Tysabri. She's vice president of Drug Safety there. She'll be followed by Dr. Craig Metz, vice president of U.S. Regulatory Affairs at GlaxoSmithKline. And he'll be talking about the Lotronex program. And finally we'll

have John Freeman from the Celgene Corporation, who'll talk about thalidomide and its STEPS program and "Revlimid and the Revlimid Assist program. So we'll start with Dr. Bozic.

DR. BOZIC: Good morning, ladies and gentlemen. My name's Carmen Bozic, and I'm the head of Drug Safety and Risk Management at Biogen Idec. First of all, I'd like to thank AHRQ and the FDA for inviting me to present here today. And I'm delighted to present to you an update on the status of the Tysabri risk management plan.

This is an outline of my presentation. First I'm going to briefly describe the regulatory background for Tysabri. Then I'll describe the RiskMAP goals, system and tools. I'll talk about how we're evaluating our plan, and then I'll conclude with some of the challenges that we've encountered.

So Tysabri or natalizumab is a humanized monoclonal antibody directed against Alpha 4 integrins that was approved in the United States for lapsing forms

of MS in November of 2004. The magnitude of Tysabri's benefit would play a significant role in its initial approval. Tysabri was approved under Sub-Part E, which allows accelerated approval of new biologics that provide a meaningful, clinical benefit over existing treatments for serious or life-threatening diseases.

Three months after its approval in February of 2005, we learned about two cases of progressive multi-focal leukrencephalopathy, which is an opportunistic infection of the brain caused by the JC virus. Within a week of hearing about these two cases, we voluntarily suspended the marketing of Tysabri and halted worldwide clinical trials. We also embarked on an extensive safety evaluation, evaluating all patients who were treated with Tysabri in clinical trials, as well as patients in the post-marketing setting.

In September of 2005, we completed our safety evaluation and determined that the occurrence of PML in Tysabri-treated patients was approximately one in a

thousand. We filed a supplemental biologics license application with the FDA at that time. In March of 2006, the FDA convened an advisory committee that unanimously recommended the re-introduction of Tysabri onto the U.S. market. In April of 2006, the CHMP similarly recommended Tysabri's approval in Europe. In June of 2006, both the FDA and CHMP approved Tysabri. And in July of 2006, we simultaneously re-introduced Tysabri into the U.S. and launched Tysabri in Europe, both with regional risk management plans.

The key point I want to make on this slide is that the unique benefit of Tysabri in a serious disabling disease, such as MS, was a key element throughout its regulatory history and a key factor in its re-approval. And just to illustrate this and the unique benefit of Tysabri, here is a slide that demonstrates the efficacy of the various MS therapies currently on the U.S. market.

So in the first row, you have the efficacy of the Beta interferon therapies, Avonex, Rebif from

Betaseron. And as you can see, they confer a reduction in relapse rate of approximately one third, and then approximately 24 to 37 percent reduction in disability progression. Copaxone or glatiramer acetate confers a 29 percent reduction in relapse rate and no statistically significant benefit on disability progression. In contrast, Tysabri confers a 68 percent reduction in relapse rate, and a 42 to 54 percent impact on disability progression.

Although it's difficult to make cross trial comparisons, it is these data that led the FDA to conclude in its Advisory Committee briefing document that the magnitude of natalizumab's benefit in relapse rate appears to be approximately twice the benefit of currently available first line treatments in MS.

MS patients played a central role in Tysabri's return. This is a picture of the over 40 MS patients who attended the Advisory Committee and gave their testimonials. Each patient spoke about the devastating

impact of the disease on their lives, about their understanding of Tysabri's risks, about the need for more effective therapies, and about the importance about making informed choices about their treatment options. These patients are what make me and my Biogen Idec colleagues work very hard to bring Tysabri back to the market and to bring it back responsibly. So when Tysabri came back to the U.S. market, it came with a risk management plan called the TOUCH prescribing program. TOUCH stands for Tysabri Outreach Unified Commitment to Health.

The risk management plan has two sets of goals, risk minimization goals and risk assessment goals. With respect to risk minimization, we want to promote informed benefit risk decisions regarding the use of Tysabri in the treatment of relapsing MS. We also want to minimize the risk of PML by re-enforcing the use of Tysabri only as a mono-therapy and not in patients who are immuno comprised.

And finally, to the extent that this is possible, based on currently available data, we want to

potentially minimize death and disability due to PML by encouraging clinical vigilance in early detection and prompt cessation of Tysabri in any patient who might have PML.

We also have risk assessment goals. We want to determine more precisely the incidence and risk factors for PML in Tysabri treated patients. And we want to assess the long-term safety of Tysabri in the clinical practice setting.

It's important to note, and we've noted this yesterday, is that risk management is a very iterative process. And the data that we are collecting from our risk assessment efforts will help us to refine and enhance the risk minimization activities over time.

When Tysabri came back to the U.S. market, it received a new indication statement. It's a two-part indication statement. The first part states that "Tysabri is indicated as a mono-therapy for the treatment of patients with relapsing MS." The indication statement has

a qualifier that says that because Tysabri increases the risk of PML, it's generally recommended for patients who've had an inadequate response to or unable to tolerate alternate MS therapies. So although Tysabri can be used as a first-line agent, it's generally recommended as a second-line agent. And we heard yesterday that many payers are restricting Tysabri to second-line use and requiring that patients fail one or more therapies before they can go on Tysabri.

Tysabri also was re-introduced with a new box warning. This is a very detailed box warning, and it's very prominently displayed. The key element of the box is that Tysabri increases the risk of PML, an opportunistic virile infection of the brain that usually leads to death or severe disability.

We also developed a robust risk minimization system that re-enforces the revised labeling. A key component of the risk minimization system is mandatory enrollment of all prescribing physicians and all patients

into the TOUCH prescribing program, which is a safety surveillance registry. Patients and physicians must read and sign an enrollment form and send it to Biogen Idec before the start of therapy.

We also have a new controlled centralized distribution system that allows us to track the location and number of all vials that we ship. And we ship Tysabri only to registered infusion centers. These are infusion centers that we've trained on the risks and benefits of Tysabri, and who have attested that they will comply with the risk management requirements. With this system, we can deliver educational tools to all prescribing neurologists, all infusion nurses who are administering Tysabri, and all MS patients who are receiving Tysabri. And then in the next few slides, I'll describe in more detail some of these tools.

An important tool that we have is the prescriber-patient acknowledgment on the enrollment form. This records that an informed benefit risk decision was

made before the start of therapy. On this form, physicians sign that they are aware of the PML risk, they have discussed the risks and benefits with their patient, and that this patient is appropriate for Tysabri therapy. The patient signs that they have read the medication guide, they've discussed the risks and benefits with their physician, and that they will report any new or worsening neurological symptoms to their physician promptly. This form must be signed and submitted to Biogen Idec prior to the start of therapy.

And here's a picture of the enrollment form. I want to clarify a misconception that arose yesterday regarding the availability of these forms. We've been purposely very careful about disseminating these forms because we've been very concerned about the potential for misuse and for inappropriate patients receiving Tysabri. So we've gaited giving out these forms to MD's who have been educated by us on the risks and benefits of Tysabri and on the risk management requirements. So I'm sorry

that it's been misinterpreted. I think it's a lack of transparency, and that certainly wasn't our intention in terms of these forms.

We also have a number of other prescriber requirements. Prescribers must report any case of PML, serious opportunistic infection or death to us promptly. They must complete a patient re-authorization questionnaire on every patient every six months and send it to Biogen Idec. On this form, they have to provide us the vital status of the patient, whether the patient has had PML or any other serious opportunistic infection, whether the patient has received any concurrent immuno-modulatory or immuno-suppressive therapies, and they have to explicitly re-authorize Tysabri dosing on every patient every six months. In addition, if a patient discontinues from Tysabri, the patient must complete a discontinuation form six months after the last dose giving us an update on the status of the patient.

We also have very stringent requirements for

infusion centers. Tysabri can be used only in registered infusion centers. These are infusion centers to whom we provided educational training on the risks and benefits of Tysabri, and these are centers that have attested to follow the risk management requirements of the program.

And these are that they can dose only patients enrolled in the program. They must give a medication guide to every patient before every dose and ask the patient to read it. They have to complete a pre-infusion checklist on every patient before every dose. This checklist screens the patient for new or worsening neurological symptoms, and reinforces its use –- the use of Tysabri as a monotherapy and not in immuno-comprised patients. And for example, if a patient reports any new or worsening neurological symptoms, the infusion nurse is instructed to contact the patient's prescriber for further instructions.

And finally, this completed pre-infusion patient checklist must be submitted to Biogen Idec within one

business day of completion. And this allows us to monitor infusion center compliance with the program, and very importantly, to track Tysabri dosing on a patient specific basis.

This is the RiskMAP as a whole. As you can see, it's a very complex program with multiple layers of controls. The RiskMAP has many components, so not only revised labeling, but the medication guide, the enrollment, the re-authorization forms, the checklists, the controlled distribution system, and a comprehensive education and training program for prescribers, infusion centers and patients. And this program provides intense safety surveillance and tracking of all patients far exceeding routine pharmacovigilance programs.

Now I'm going to be talking about how we've been evaluating the success of our efforts. So worldwide in both commercial use and clinical trials, about 12,000 patients are on Tysabri therapy since it's re-introduction in the summer of 2006. In the U.S., we've dosed about

8,000 patients. In Europe, we've dosed about 3,000 patients, and we also have about a thousand patients enrolled in Tysabri clinical trials. The worldwide cumulative exposure in clinical trials and commercially is approximately 21,000 patients.

Now looking more closely at the TOUCH enrollment here in the U.S., about 11,000 patients have enrolled into the TOUCH program of which about 8,000 have been exposed. The median exposure is about four doses at this point. Only 3 percent of patients are naive to MS therapies, so 97 percent of patients have received at least one or more MS therapies before going on Tysabri. Seventeen hundred patients have enrolled –- 1700 physicians have enrolled patients, and 1700 infusion sites have been trained and authorized.

Here is some process metrics that we've been monitoring very closely with respect to the program. So 99.9 percent of the infusions are to patients that have been enrolled in the program. What this tells us is that

patients and prescribers are making informed decisions about the risk of Tysabri because a prerequisite to enrolling in the program is signing the prescriber-patient acknowledgment. 96.8 percent of patients are receiving Tysabri without any concurrent immuno-modulatory or immuno-suppressant therapies. What this tells us is that Tysabri is being prescribed overwhelmingly as a mono-therapy according to the label.

99.9 percent of the over 10,000 drug shipments that we made have been shipped to authorized infusion site. And finally we've received 99.9 percent of the almost 40,000 checklists that have been completed to Biogen Idec. What this means is that the system is reinforcing the importance of clinical vigilance which may lead to the early detection of PML. So across multiple dimensions, compliance with the program has been truly excellent.

And I want to say that we take any instance of non-compliance extremely seriously. If we hear about a

case of non-compliance, we investigate it thoroughly, we try to understand it's root cause, we put in a corrective and preventive action plan in place. And if there's instances of recurrent non-compliance, we have de-enrolled certain participants from the program.

We've also done surveys of prescribers and infusion nurses to understand –- whether they understand the key learnings about the program. And what we've concluded is that the awareness of PML risk is extremely high amongst the program participants. So for example, 99 percent of prescribers understand that Tysabri is associated with an increase risk of PML. And 100 percent of nurses know that Tysabri should be administered only to enrolled patients.

The majority of the participants also understand the key components of the program. For example, 98 percent of prescribers understand that they have to report a case of PML to us. And 99 percent of nurses know that they must contact the patient's prescriber if the patient

reports any new or worsening neurological symptoms. So indeed I think the program has accomplished a very high level of PML awareness amongst its participants.

From a safety outcome's perspective, the long-term safety data at this point are still limited. But to date, we've had no new confirmed cases of PML or other serious opportunistic infections worldwide. And the post-marketing safety profile is consistent with what we've seen in clinical trials.

Now I'll turn to some of the challenges that we've encountered in implementing and conducting this program. So our first challenge was implementing what is one of the most complex and comprehensive risk management plans ever developed. And across multiple metrics, we can say that the implementation has been successful. As you can see, compliance with a program is indeed high. Tysabri appears to be used in appropriate patients as a mono-therapy, and the awareness of PML risk is very high as well.

We have several factors that we attribute this success to. First of all, we have very motivated MS patients and very motivated neurologist prescribers. MS itself is a very serious, disabling disease, and there's a high need for more effective therapies. We have extensive experience in the MS community.

We have –- our other drug Avonex has been marketed for over 10 years. And we leveraged our existing system for patient and physician support, and we leveraged that to help support the Tysabri risk management plan.

We also applied very significant company resources to ensure a successful implementation. And we provided very intensive training and education of prescribers and patients and infusion centers. And we believe this component of the program is indeed very, very important.

On the other hand, we've had some challenges in communication. Under Sub-Part E, our ability to provide the most up-to-date safety data is limited. The number

one request we get from prescribers and patients is give us the most up-to-date safety data on Tysabri, and specifically how many patients have you treated, and have you had any cases of PML. And so we really want to provide that, and we do that in the settings of major medical meetings periodically. However, we want to be able to do that in a much more real time fashion because after all, the TOUCH prescribing program is designed to collect real time safety data. On the other hand, all of our communication materials, including the dissemination of this type of safety data, must be pre-reviewed by the agency. And this does lead to some delay.

The second challenge we've had in terms of communication is that our benefit risk message has not been balanced. So as you can see from my previous slides, I think we've done a very good job of communicating the risk profile of the drug. And the understanding of risk is very high in the community. On the other hand, our success in communicating the benefit profile has not been

as great. And I attribute that to the fact that risk management programs are really inherently designed to communicate risk. And perhaps we need to be thinking more in terms of benefit risk management programs and communicating both sides of the equation in a more balanced way.

So just to give you a metric around the benefit messaging, 70 percent of patients when we surveyed them didn't understand Tysabri's benefit. So we think it's very important to consistently communicate both the benefit and risk around products with risk management plans because the alternative is that patients may consider other perhaps unproven therapies for MS.

We've also seen the emergence of some unintended consequences. So for example, what we've seen from our enrollment data is Tysabri is utilized much more frequently in large care centers compared to small neurology practices. And what we've been hearing is that the large centers are able to apply the necessary

resources to implement this type of program.

When we've surveyed physicians, we've also heard feedback from physicians that many of them have said that the program may prevent patient access because of the administrative burden to their practice. Physicians have expressed to us some liability concerns around some of the statements on the prescriber-patient acknowledgment. And we heard yesterday from Mrs. Bloom, the MS patient, that there seemed to be perhaps some coordination difficulties between drug delivery and patient scheduling that have affected some of the patients in terms of their ability to get Tysabri treatment. So we take all of this very seriously.

And what we are noting is that there are some limitations to patient access to Tysabri. So we do see some opportunity to streamline some of the redundancies in the system while at the same time still protecting the public health and maintaining a very robust risk management program. So, for example, again we heard

yesterday that I think the process to switch infusion sites is confusing to patients. And it turns out MS patients are a very mobile patient population, and they do switch their infusion sites at a fairly high rate.

The current system for switching infusion sites is very complicated, requires a lot of communications, a lot of faxes. And we've put in proposals to the FDA about how to make that much simpler and more patient-friendly. And we'll be meeting with the FDA in the near future to discuss these types of streamlining proposals for the program.

And my last point is that I think it's very important that we have a very clear mechanism to engage the FDA in the RiskMAP evaluation process. The process for RiskMAP evaluation as we've heard yesterday, and I think we'll hear today, is very unique and it's very dynamic. And it requires interaction with many FDA divisions, the Review division, the Office of Surveillance and Epidemiology, DDMAC, for example. And I recognize

that every drug requires multiple FDA interactions, but the interactions that we have of risk management plans are sort of at a different level of complexity. And so it would be very important to have a single point of contact at the FDA to facilitate these interactions.

The other concern that we have is that there are no clear time lines in terms of engaging the FDA to make changes to the program. For example, even to make small administrative changes, there really isn't a framework in which to do that expeditiously, let alone more major changes. So I think it would be very important to have clear mechanisms and time frames to engage the FDA and to get their feedback on the ongoing evaluation and refinements to the risk management plan because it is indeed a very iterative and dynamic process.

So finally, Tysabri confers a unique benefit in relapsing MS, which is a serious and disabling disease. We've successfully and responsibly implemented a comprehensive risk management plan. RiskMAP evaluations

and enhancements require a new mechanism for FDA interactions post-approval. And we think it's very important to communicate real time safety data and balance benefit-risk information to the public.

So I'd like to in conclusion say that I believe it's very heartening to see that we are collectively evaluating our risk management efforts in forms such as these. And I believe these types of discussions will enhance our ability to develop and implement appropriate risk management plans that are commensurate with the risk-benefit profile of the drug without limiting patient access to important therapies. Thank you.

DR. DALPAN: Okay, we'll save the questions to the end, and we'll have Dr. Metz now talk about Lotronex.

DR. METZ: Okay. I'm going to talk to you today about the Lotronex risk management program. And as some of you might have imagined, it's been a very intense learning experience for us as far as trying to manage risk in a primary care setting. At times the intensity of that

experience has been such that it might cause somebody to seek psycho-therapy or counseling, but enough about me. Let’s just move on.

These are the topics that I’m going to cover today. And just a public health warning. The opinions that I express, and for any of you that happen to know me, I have plenty of those, are mine and not GSK’s or any of its various incarnations.

So here’s just some information on the background and some of the significant events in the life of Lotronex. It was launched in March of 2000, and subsequent in November of that same year, had to be withdrawn from the marketplace because we reached a point where labeling interventions were not sufficient enough to change the kind of behaviors that we were seeing in the prescribing community. Immediately thereafter, both the FDA and GSK were inundated with calls and communications from patients who said that this drug had made a significant change in their life and they wanted it back

on the marketplace.

Because of that, GSK and the FDA worked together, and SNDA was subsequently submitted that led to the product being reapproved under Sub-Part H in June of 2002 and subsequently re-introduced into the marketplace in November of 2002 under the auspices of the risk management program that I'm going to describe to you in a moment.

What's interesting to note here is that many of the interventions in the RiskMAP guidance that came out in 2005 were actually incorporated into the Lotronex risk management program, 10 or 11 out of the 13 different interventions. So what that gives you is a very interesting opportunity to look at how these interventions affect product use in a primary care practice setting.

So here are the goals for our RiskMAP. Quite simply, to reduce the risk that led to the product being withdrawn to begin with, serious gastrointestinal events, ischemic colitis, and complications of constipation. And

importantly when those events occurred, have a system in place that would prevent the serious outcomes that were associated with those events prior to product withdrawal. And here's the tricky thing. Making sure that we did this in a way that didn't deny access to the product the patients who really were appropriate for therapy.

So what were we trying to do with the program? Really we were trying to impact prescriber and patient behaviors. We wanted to make sure that the people prescribing Lotronex were well aware of the key information regarding appropriate product use. And we wanted to make sure that the patients receiving the drug were appropriate for therapy. And these were things that weren't necessarily prevalent during the initial marketing period.

And we wanted a patient education program that would not only make the patients aware of key product use information regarding benefit and risk, but also aware of the action that they needed to take should they start to

observe any symptoms related to some of these events that caused the product to be removed from the marketplace. And then finally, aggressive proactive reporting and collection of adverse events.

So here are the tool kits, the buckets of interventions that the FDA has identified in its RiskMAP. And in the next few slides, you'll see a banner running across the bottom with relevant quotes from the FDA's RiskMAP guidance. And I'm going to describe some of the individual components of these tool sets that were incorporated into the Lotronex risk management program.

And again as Carmen has mentioned, a RiskMAP is a very dynamic living thing. It requires continual evaluation and revision. We've made a number of course corrections with Lotronex program across time. So we wanted to evaluate in real time what the tool performance is, and importantly, how those tools have impacted the prescribers and the patients. And then finally, are the critical messages being delivered? Are people being

compliant with the important processes and procedures that we've outlined in the prescribing program for Lotronex and the risk management program itself.

So here are some of the key components of the prescribing program for Lotronex –- revised labeling, enrollment of qualified and informed physicians, patient counseling. Again we tried to stress and emphasis and provide every opportunity for that important discussion between the patient and the practitioner. Compliance with a program reinforced by pharmacists. I'll come back to that a little bit later, picking up on the themes yet from yesterday about how we involve our pharmacy colleagues or perhaps don't at times. Education and training. And again, the importance of reporting and collecting adverse events. And finally, this critical element of continual program evaluation.

What are the key labeling features for Lotronex following its re-introduction? Has a black box warning, has a modified indication that I'm going to describe to

you in a moment. It has updated risk and benefit information included in patient information medication guide. We started with a lower starting dose than the initially approved dose. The reason we did that was to make sure that we didn't have patients taking the drug who were going to be hypersensitive to it and immediately start to get in trouble with constipation. And we provide them an opportunity to actually have efficacy at a lower dose or titrate to a higher dose if they were tolerating the drug. And then obviously a critical medication guide for the patients.

So what does this modified indication statement look like? The drug is now approved for women with severe diarrhea predominant IBS who have chronic symptoms described as generally greater than six months where you've excluded other GI abnormalities, and these patients have failed conventional therapy. And importantly, we define severe as having these qualities: frequent and severe discomfort, frequent bowel urgency or disability

restrictions, the daily activities of daily living. It's really important to note the aura that follows each of those statements. A patient was not required to have all of these things to be appropriate for therapy, but just one. We'll come back to that.

As far as education is concerned, we had a very comprehensive educational program. We mailed tens of thousands of letters to physicians and pharmacists describing the prescribing program for Lotronex and the conditions for its re-introduction to the marketplace. We had a number of information programs for healthcare providers, the medication guide we've discussed. We had a patient guide for physicians to use to assist them in counseling patients. We had a call center with people who were specifically trained on the prescribing program for Lotronex that physicians could call and ask questions about the program, how to obtain prescribing kits and other information. We also had an active website, and there were other things that involved symposia at

professional society meetings. So very significant education and outreach program.

A number of reminder systems were included in the Lotronex risk management program. The most prominent of which was a requirement for a physician who wanted to prescribe Lotronex to enroll in the prescribing program for Lotronex. That required them to sign an attestation form which said that they had the ability to diagnose and manage IBS ischemic colitis and complications, the constipation that they would be compliant with the prescribing program for Lotronex, and that they would indeed report all serious adverse events.

There was also a patient physician agreement, a patient consent document that both parties had to sign to again attest to their understanding of the critical product information, and also attest to their intent to report information to each other and to the FDA or GSK as needed. And the ever-present prescription stickers. Again, I've been talking to some other people. I think

it’s like collecting baseball cards. If we can get a complete set of prescription stickers across these programs, what would that be worth? The prescription stickers again were there to identify all interested parties that this was coming out of a RiskMAP program, and that sticker on that prescription indicated that a number of processes had been followed.

And then the final three things. The hard copy, the only prescriptions, no facts, no telephone, the drug was only packaged in bottles of 30, and there was additional specialized packaging. The intent on those last three things was to force the patient back to the physician on a regular basis, and again, to drive those important discussions about how the product use is going and how they should move forward from that point.

Our program evaluation objectives really are quite simple. Are we moving –- are we getting –- achieving our health outcome goals? Are these tools, these interventions, really driving the realization of our

objectives? Are the physicians qualified and informed? Are patients who are really –- had the opportunity for the most benefit and least risk being treated? And are they informed about those risks and benefits? And then finally, what kind of unintended consequences are we seeing?

The evaluation strategy was to look at adverse events with special interest. Again, ischemic colitis, serious complications of constipation. We have an assessment program for prescribers where we purchased a national prescription database and compared the database of all prescribers against our database of prescribers enrolled in the prescribing program for Lotronex.

We have a voluntary patient follow-up survey program, which I'm going to describe. And then we had a very comprehensive longitudinal claims base observational study program that had about nine million covered lives in it. And the intent of that program was to have a retrospective look through case review at were these

patients really being appropriately treated. When issues would arise, what action was taken, and what were the outcomes.

So this is the Lotronex risk management program. You know, this represents the efforts and well intentioned thinking of a team of people at the FDA and at GSK about four or five years ago when we were really working without a net. We really didn't know what the impact of these things would be, and we felt this was a reasonable program to move forward with.

So let's just take a look at where we are with things as of June of last year. And unfortunately, things don't change much with Lotronex, so the June data of last year is about the same as the June date of this year.

Importantly, we're seeing no new safety signals. And when we have seen cases involving the adverse events of special interest, those cases are qualitatively similar to what we've seen before. But very importantly, we're seeing generally less severe outcomes associated with

those events when they occur. And in the cases that we have been able to review through chart review, what we're seeing is prompt action on behalf of the patient and the physician. So it looks like some of these key messages are filtering themselves through to clinical practice, and that's important.

So we believe there's a high unmet need here. Yet we've got very little prescribing rate. Research shows that the potential target population of severe IBS patients should be something between a thousand –- 100,000 to 2.9 million. Yet what we have up until May of last year is 21,200 patients treated. That is very low level of product uptake, and you really wonder what's going on there.

Well, what about the physician roster comparison? When we compared the database of all prescribers against our prescribing program for Lotronex, what we've seen across time is that anywhere from 84 to 88 percent of the prescriptions are coming from physicians

who are in that prescribing program for Lotronex. And I think in a setting where you're not in restricted distribution, it will be very difficult to beat these numbers. Normally regulatory people are not very cheerful people, but these numbers put me in my happy place.

So when you couple this with the fact that we're not seeing any new signals when we look at our cases, and that part of the data looks similar to what we've seen before, and you look at this high prescribing rate within the prescribing program for Lotronex, those two things together give you pretty good comfort that the program is doing what we wanted it to do. I'd suggest that if that

prescribing line was down around the 50 or 60 percent level, we might be having some different discussions with the agency. Or if it was, where is it is right now and we were seeing events associated with prescribers prescribing outside the program, we'd be having discussions. But neither of those are the case.

Well, what about this patient follow-up survey program? So the objectives here –- we're really going to try to get to the patient level and understand what they understand about the risks and benefits associated with the use of Lotronex, and look at the compliance with the prescribing program for Lotronex. Are the processes being followed? And then finally, should the patients have received the drug?

Well, here are survey enrollment figures, and these have been fairly constant across time as well. Twenty-nine percent of all patients receiving a prescription for Lotronex who are in the program have

completed the baseline survey. Now we've had some criticisms about, well, gee, that's a very low rate. Well, not when you look at voluntary surveys. This rate is fairly consistent with the voluntary survey context. The question then becomes are these representative of all the patients receiving Lotronex. Now that's very difficult to demonstrate. We've done some regional analyses and some other types of subset analyses, which doesn't give us any reason to believe that they're not representative, but we can't prove that.

Well, who are the patients that have completed this survey? Ninety-three percent of them are female, 7 percent male. You have to remember that males were not contra-indicated for use. They're just not indicated for use. And oddly enough, when the product was withdrawn, male patients were some of the most vocal patients that we heard from.

What's really interesting here is what we see as female, Caucasian patients with at least some college

education. While we believe that the people enrolled in this patient follow-up survey are representative of people receiving Lotronex right now, I really wonder whether this is representative of the patients that have severe diarrhea predominant in the IBS. It’s a little suspicious

to me.

Well, what about compliance with the prescribing program for Lotronex? Again we're very pleased about this. Ninety-one percent are signing that patient-physician agreement. And I think that's one of the more critical components of our whole program because there's just something about a patient having to sign something that says I understand how I should use this product. And I understand what I should do if something starts to happen to me. I think that's pretty powerful. They've discussed –- 97 percent have discussed with a physician how Lotronex can help them, and about the same number have discussed with a physician what to do if something bad starts to happen.

We put a number of places in there where they would receive a medication guide. The physicians were to hand them out. Pharmacists –- and they're also packaged

in that special packaging that I was telling you about. So again it would be very difficult for a patient to get a prescription for Lotronex and not run into that medication guide someplace. And if they did get it, 98 percent of them said they read it. Again that's what we want to have happen. That's the behavior we were looking for. And most of them recall seeing a blue sticker someplace.

But what about their appropriateness for therapy based on survey results? Again very good for a setting that didn't involve a restricted distribution and those types of programs. Ninety percent met the treatment and severity criteria. What's really interesting is the majority of them, almost three quarters of them, had all three severity conditions. And I remind you a moment ago that they're only required to have one. Well, what does that mean? It looks like treatment is being reserved for only those patients at the most severe end of the severe spectrum. That was not the intention of the prescribing

program or the labeling. But it looks like that's where the clinical practice has gone.

Well, unfortunately, we ran into a problem with the longitudinal claims-based observational studies because the viability of those programs is dependent on significant product uptake. And we haven't had that. And in fact for us to get to the point where we'd be able to make any inferential analyses around the data coming out of this program, at the current rate of product uptake, it would be something like another nine or 10 years. So we've put this in the suspended animation, and we'll see what happens.

Okay. So what about some key learnings? Well, you know, we've talked about this a little bit already yesterday. When you're putting these programs together, you need to be conscious of the potential impact on the prescribers. This physician attestation process causes a number of prescribers a bit of anxiety. Somehow or

another they believe that it's a subtle transfer of liability from the sponsor to the practicing physician, a unique transfer of that liability. And you've heard comments like this before. An affront to professional training, a duplication of the licensor process. These comments are pretty consistent across RiskMAP programs where there is some element of attestation. I don't know if this is a particularly useful intervention from my point of view. The idea here is that they be educated, and that they be aware of what they need to do and how they should prescribe the drug. And if we can get away from this attestation word somehow or another, I think they'll be a little happier.

But what's really important, the really critical thing, is to understand the impact of the risk management program on a clinical practice paradigm itself. What is that time and paperwork burden, and how might that produce an inappropriate barrier to patient access? Well, this is

not a Parker Brothers board game. This is the flow diagram for the prescribing program for Lotronex. There are a number of steps here. And it's a logical process, but when you take a quick look at it, your initial reaction, if you're a prescriber, is to go, oh, my gosh. Look at all this. And I think again it's a communication issue. You need to be careful about how you produce these types of flow diagrams, or you're going to get that kind of visceral response from people. And I'll come back later on to the yellow part here where we talk about what we ask the pharmacists to do.

Here's another potential indication of some kind of a barrier to prescribing. First of all, the number of prescribers who have registered to prescribe Lotronex is an order of magnitude lower than the prescribers who were prescribing the product during initial approval. But what's interesting is of the 7700 who have enrolled, only half of them have chosen to write a prescription. So

again you wonder what's happening there. They register for the program. They get the prescribing kit, and then they don't prescribe. What's going on there? Is it they look at this and say, oh, no, not here. I don't have the time for this. It's too burdensome. It would be interesting to know.

We've done some focus group work with patients who are prescribing –- physicians who are prescribing, physicians who used to prescribing and aren't prescribing. The messages that we get are a burden. They're an all around burden. It takes me 20 or 30 minutes to get one patient through this process, maybe longer, and I only have five minutes. I want to be a physician, but I'm in a business as well. So you hear that tension coming out in those focus groups.

Well, at the patient level what you have to be concerned about is this very delicate balance between informing a patient and frightening them. So as you've

heard before, our RiskMAP program is no different than the others. The focus is almost exclusively on risk. And if you read the medication guide and the patient-physician agreement for Lotronex, it doesn't leave you in a very happy place. And it's really only the most resolute patients who are going to say all right, all right, I'm going to take all of that risk, and I'm going to try the drug anyway. So again we've got to get more balance into that.

And we've got a requirement here to sign, this special document, this patient-physician agreement, which is something patients aren't used to doing, so that's a little frightening to them. And the interesting thing is we know a lot about patients who are taking the drug, but what we don't know about in clinical practice is patients that aren't taking the drug, patients who've had the discussion with their physicians and have walked away from that without a prescription. Well, interestingly enough,

we're doing a series of post-marketing commitment studies, things which we do take quite seriously. And we have some data coming out of that that's of interest.

The consent forms and the information that we use for those studies is very similar if not identical to what we have in the medication guide. And what we've found out is that 28 percent of the patients who were considered appropriate for therapy and study inclusion by their physicians, refused to participate in the study because they said, "They were frightened by the information and afraid to take the drug." So that is some interesting data. And again, it tends to suggest that we need more balance in the way that information's presented.

So just some parting thoughts. It's very important to proactively discuss and agree the RMP goals and associated actions. So scenario planning is something we did not do very well with Lotronex. We got our program out there, and then retrospectively tried to understand

what to do if things happened. Scenario path planning is critical. If we get to this point, then we do this. And it's not just uni-directional. There should be a point at which you can get relief from some of the elements of a risk management program. It can't just be more and more burden. And you need to agree to those things up front as best you can.

We talked about balance communication. And again poor product uptake because of an imbalance in the way information is communicated can't really be viewed as an unintended consequence anymore. We know what the impact of that is. If we don't handle that or manage that communication better, it is an intended consequence.

The disease setting has a definite impact on risk management program's success. Again looking at the Tysabri program, you've got a captive patient audience. This type of a process, although, you know, somewhat cumbersome fits better into a specialty prescribing

program where the patients have to come in periodically to get their drug, than it might in an outpatient primary care setting. So again I think you need to be cognizant of the impact of the disease setting and the care setting on your opportunity for success or the burdensomeness of your interventions, and proactively engage all stakeholders.

Again I take you back to that flow diagram that we have. Yeah, we mailed a lot of stuff out to pharmacists about what we were going to do with the prescribing program for Lotronex. But what we let happen was they get the prescription at the end of that conveyor belt, and it has a sticker on it. Okay, that's fine. Then they prescribe the product and everything is cool. But what if it doesn't have a sticker on it? Now what do they do? Do they fill the prescription and think that they've done something illegal by doing so, or do they call the gastroenterologist and say I'm not going to fill

your prescription. You shouldn't have written it. That's just a lovely dilemma for pharmacists to be in.

We had a number of phone calls about that, and the ones that I got didn't start out with thank you. So if we're going to make people part of the program, make them part of the program. Get the key stakeholders together and say this is how we're going to do that, how do you want to manage it.

In assessing interventions in real world conditions, we talked a little bit about this yesterday. I think wherever possible, you ought to try to embed some of these things into Phase III. And I think at a minimum, we need to do more work on labeling comprehension at the patient and prescriber level. Here are the key messages from our product labeling. Do you understand these, and what would you do. And I think we've got to do more work about that. And I think a lot of this risk can be controlled with just some labeling comprehension work

during Phase III.

And then the final question is how relevant is Lotronex to other situations? I think you can't forget the potential impact of the fact that this drug came off of the marketplace and was reintroduced, and the confusion that that created and the confusion that's still present. As recently as a couple of weeks ago, I saw an article that said pretty emphatically that Lotronex patients could only receive the product following re-introduction if they'd had it before the product was withdrawn from the marketplace. Let me think. No. That's not right. So we had to seek a correction on that. But that's four or five years out, and we still have that kind of confusion. So I think again you have to be cognizant of the fact that this is product that came off the marketplace, came back on the marketplace. And I think the message here is it's best to avoid that for your programs. And with that, in the interest of your mental health, I will stop.

DR. DALPAN: And finally we'll hear from John Freeman from Celgene.

MR. FREEMAN: Thank you. This is stressful. Not because of speaking to a room with perhaps a couple of hundred people present or an unknown audience on the web. No, this is stressful because we have Hugh "Letterman" Tilson in the room hanging on to your delivery looking for sound bytes that will then magically appear on a slide in conclusion. So Hugh, if you're interested in a bathroom break, please can I encourage you to take it now.

My name's John Freeman. I head drug safety at Celgene, and I'm pleased to be talking with you this morning about the company's experience in managing the RevAssist and STEPS programs. I'm pleased also that many of the slides and materials that I'm going to be talking about were previously introduced by other speakers yesterday. And so that can speed up my time on the podium.

I appreciate the opportunity to speak. But I'd also like to reach out and thank the agencies for initiating this two-day meeting. I think anything that we can do to ensure understanding concerning RiskMAPs, what they mean, what they translate to in terms of impact to the stakeholders and participants, and how they might fit downstream I think is extremely valuable.

STEPS is perhaps the flagship risk management program. It was initiated in 1998 and covers thalidomide. RevAssist was initiated at the end of 2005 and includes Lenalidomide or Revlimid. Revlimid, an analog of thalidomide, structurally distinct. Doesn't share any of the metabolites of thalidomide. Some overlapping pharmacology, but that's perhaps where the similarity ends.

The experience that we've had with now over 18 months on the market is perhaps one of a distinct safety profile. For example, we're not seeing neuropathy at the

same level in severity as is typical of thalidomide. And more significantly, there's currently no evidence that Revlimid induces the fetal malformations that are typical of thalidomide. And yet what you'll hear me describe in terms of RevAssist and the risk management program is almost an entire duplicate of the STEPS program.

I speak on behalf of Celgene and the almost 200 staff members who are engaged full time in managing these two programs, and represent the dedication those individuals translate to the program and to making both programs successful.

If there are two key take-home messages and perhaps two sound bytes for Hugh, it would be that effective, highly effective risk minimization is possible through a program of augmented control distribution. And secondly, that that is so, reflects the achievements and contributions of the patients, prescribers, pharmacists and the company in making that happen. I cannot

underscore enough the importance of having the right corporate culture for ensuring that these risk management programs prevail.

As a recent migrant to these shores, it took me a little while to understand what I heard from Texas in terms of their favorite mantra, don't mess with Texas. And it was only after I visited Houston –- yeah, I understand. Similarly after joining Celgene, it took me a little while to understand their mantra, don't mess with STEPS. Now I get it. Why? Well, this is why.

This slide, it's image is being seen by many. It's included in the materials that patients and prescribers who are participants within the STEPS program and RevAssist program see. And you might think given the notoriety of thalidomide and its experience, some almost 50 years ago now, that it might be relatively simple to ensure that such outcomes didn't occur today. For example, in Brazil, the manufacturing of thalidomide is

undertaken strictly by the Brazilian government. There is a controlled distribution program that involves patient education and restrictions on prescriptions. And yet infants are being born in Brazil and other places around the world today with the same problems that we saw almost 50 years ago in many other parts of the world. So what stands between thalidomide here in the U.S. and outcomes of that type here in the U.S.? The answer is the STEPS RiskMAP program.

What I'd like to do over the remaining 15 minutes or so is to talk with you about the objectives of that program, how it operates, how we, with the partner groups involved in STEPS and RevAssist, ensure their effectiveness, to share with you some of the key operating metrics, to actually look at just how successful these programs have been, to talk about some of the unanticipated up-sides and down-sides of those programs, and then to offer you some parting thoughts in terms of

our experience and perspective.

So where do these programs actually sit within the range of options in terms of risk management? I think it was interesting yesterday to hear the –- that perhaps there wasn't a consistent understanding as to what RiskMAP programs entail. There isn't a single RiskMAP entity. It's clearly situational. It depends upon the particular drug, the particular setting, the particular risk.

STEPS and RevAssist focus on managed distribution, performance-based distribution, augmented by a series of measures that ensure effective risk communication, education, counseling, and patient qualification. The two programs are almost identical. Celgene only has two products really, Thalomid and thalidomide. If the company had another slogan, I think it would be RiskMAPs are us.

The goals of the program clearly avoids fetal exposure. In the case of RevAssist, there's an additional

goal, that of managing neutropenia and thromboside apenia associated with Revlimid through the effective education of prescribers and patients.

Educational. Talk about active risk aversion. That's something which I think is –- I suspect is unique to the Celgene organization. Essentially we have real time monitoring of the effective application systems measures. And we have a team of risk intervention specialists. I think they perceive themselves as rather like Superman with (indiscernible), jumping into the nearest telephone kiosk and zooming off to sort out problems in real time with the program. If you get a call from these guys as a prescriber, they will help you.

So in looking at the operation of the two programs, the first stopping point is compulsory registration, prescribers, patients and pharmacies. That seeks to ensure effective counseling of patients, a signed patient-physician agreement form generated to confirm that

the appropriate discussion has taken place between prescriber and patient, pregnancy testing, the understanding and adoption of effective contraception. Then only when a certain sequence of those events occurred in succession, each step qualifying the next step, is a prescription authorization creates it within the system. And then finally product release.

But there is an intervening step, that of the mandatory survey process. Prescribers and patients have to work within the survey system and satisfy us that they have performed all these conditions before then we will release the prescription. The company's positioned in a way that if they intervene and block prescription release, unless all of those conditions are met. So the message to prescribers is you've got to do it, you've got to document you've done it. You've got to tell us you've done it. And then by the way, we're going to come back and then recheck that you've done it.

But this all doesn’t happen through some pull of gravity, some goodwill. This happens largely because the company is in the background ensuring that it happens. This process is the business model of Celgene. This process proceeds effectively. It is the concerted efforts of almost every single group within the company operating in concert starting with senior management represented within the risk management committee, the customer care group who are the active recipients of the various calls and registration interactions, risk intervention. I’ve mentioned will reach out and ensure that any received breach of compliance is rectified, the technical operations group, who then ensure that the prescriptions are appropriately filled through a program of distribution. And again once all of the qualification is met, the field force are out there educating prescribers and to resolve the program’s elements, the Drug Safety group who pick up a very high volume of adverse event

reports created by the interactions between prescribers, patients and this program. And then finally the Compliance group who will on a periodic and as-needed basis naturally go and physically inspect the participants in this process to ensure that it's working effectively.

It was interesting yesterday to hear some talk about flexibility, and the suggestions by some groups that RiskMAPs ought to be flexible. This ain't flexible. This is rigorous. This is burdensome, yes. But when you actually appreciate what it is that the company is trying to ensure it achieves, you can understand why we don't go for flexibility.

Okay, I'll skip through many of these slides because I think they were introduced yesterday. But the whole process starts with patient risk classification, patients are classified into any one of the following six groups based on their pregnancy potential, females, males, child-bearing potential or not. And this classification

then does drive elements of the resulting program and risk intervention measures.

In terms of pregnancy prevention, really quite rigorous in terms of defining what constitutes effective contraception. And again these elements are captured within the mandatory –- other surveys that are conducted throughout the course of the program. Pregnancy testing before, during, during treatment interruptions and four weeks after completion of therapy.

No more than 28 days worth of drug is issued. There were no automatic refills. So significantly what you've just seen in terms of the elements of the process that patients and prescribers have to go through. They have to go through every single month. So you can sense that the number of interactions, transactions between the prescribing environment, patients in the company is intense. It's estimated that for any one prescription, there are as many as five to 10 fax, telephone or IVRS

interactions between the prescribers, patients and the company.

Mandatory patient service I mentioned occur both at the time of initial prescription and the time of repeat prescription. Many are done through calling into the customer care center. The remainder are done through IVRS. In any one instance that a patient or prescriber doesn't answer the question correctly, the prescription is blocked, and the company reaches out to the party to better understand the situation.

So in terms of the key operating metrics, well, this is perhaps my watering in terms of what this actually translates to over the last eight years of STEPS operation. In fact this data was up to the end of 2006. Almost now one million prescriptions have been issued through the STEPS programs. That's one million of these. Perhaps between five and 10 interactions between patients, prescribers and the company.

The most important key operating metric is that the midst that one believes the prescriptions that have not been on our watch a single in utero exposure resulting in congenital malformations associated with thalidomide, something that we're proud of, and something that we know the prescribed base ultimately is subscribed to.

I mentioned the voluntary surveys. These are performed in addition to the mandatory surveys that are performed on a sample of participating patients. These data are from RevAssist. The surveys are undertaken by a third party organization, and the results of the survey are reported either quarterly or semi-annually in a report directly to FDA. The survey indicates a very high level of understanding of the program objectives. And importantly in instances that it's implied that patients that didn't understand fully the question that was posed, we are able to reach out to them. And in most instances, you're reminded that we're dealing with oftentimes an

elderly population, who perhaps didn't automatically understand the question that was being posed.

In terms of up-sizing and other consequences of the program, as somebody's who's worked in drug safety for a long time, I luxuriate in the quality of the data that we receive through this program. We don't have to estimate exposure. We have very, very precise prescription drug utilization information that enables us to understand how the product is being used, when it's withdrawn with the patient's interrupt treatment, with the patient's move from Thalomid to Revlimid, back again, where they actually go in the country. It really is quite wonderful.

Also as an adverse event's jockey, I really have a lot of time. Brian, if you're still with us, this moves us more towards data than anecdote. There is a very high safety report involving the (indiscernible) of these programs if you consider that most prescribed products,

you’re looking at a 5 to 10 percent reporting incidence. We’re anywhere up to 30, 40 percent in some settings.

There is a downside, though, and there’s a new metric term which is I think broadly entitled prescriber A reporting syndrome. There is a –- for prescribers who are already active within his program do provide us with a lot of information. They aren’t always terribly receptive when we try to follow up on the A reports. It’s also significant I think to distinguish what we’re seeing in this A report and setting for (indiscernible) convention a distributed product, and we’re still subject to the same spontaneous reporting rules. And that’s something what I’ll pick up in the end.

But what are the impact? A million prescriptions for Thalomid over an eight-year period. That translates to for every office hour, every 10 seconds sees an interaction, whether it’ll be fax, phone or other between prescribers, patients and ourselves. The average

data call volume as you can see here runs to about 1300 calls per day.

So Celgene's overall experience and perspective, highly effective risk minimization through control distribution is most definitely possible. It creates a considerable burden on the involved parties. To do it properly requires considerable industry expertise, resolve, determination, an ingrained culture of risk management central to the company's philosophies and values.

Also RiskMAPs must be proportionate to the perceived level of risk. Clearly in the case of thalidomide, that isn't an issue. But as we perhaps look at other products and therapeutics settings, that's something that we'd like to explore. Similarly it should be possible to adjust some of the methods and emphasis based on variation in risk profiles across the patient sub-groups.

To the point, I made earlier about AE reporting, controlled distribution RiskMAPs isn't the norm. And perhaps there should be easement in some areas of regulatory requirements compared to conventionally distributed drugs.

And then I think echoing some of the comments from the immediate preceding speakers, these programs are iterative. They evolve with practical experience. They require fine cost adjustment along the way. And yet every single time that we want to make even the most modest of changes within these programs, we have to seek prior regulatory approval before that actually happens. That can take a very long time.

So in parting, I hope I've conveyed to you that performing effective risk minimization programs is not a demonstrative function. It's something that takes passion, commitment and drive. It creates a considerable burden on all of the involved parties. I think recipes

for success probably revolve around having an effective product, an unmet need, and a grievous illness, and then 110 percent commitment for all concerned. Thank you.

DR. DALPAN: Okay, if I could ask each of our three speakers to come up here. And for anybody with questions, wind up at the two microphones, and we'll –- Brian, you want to start?

DR. STROM: Yeah, I would like to thank the three speakers for excellent presentations. And I found the contrast between them very, very useful and important. I think it's also important to realize the contrast and the purpose of the three RiskMAPs. And I think as we move to evaluation this afternoon, it's very important to keep that in mind.

Again my comment, the question is what is the question. In some cases, the goal is to decrease exposure to people who you can identify are high risk. In some cases the goal is to increase exposure to people who you

think are likely to benefit. But sometimes you can't tell, and the goal is just to decrease exposure. And so in the Lotronex example, I thought we did hear a lot of comments, and I would use the word complaints, about the burden.

I would argue the burden is the total purpose of the program. And the goal is not to decrease –- you would not want to decrease the burden, and you would not want to pull product uptake, which you complained about, is in fact the goal. This is a product –- this is a condition that in principle is present in 20 percent of the female population. And this is a drug that could be extremely widely used. The fact that it is used in a very narrow way and only in sick people as you demonstrated shows the success of the program. And so when it comes to looking at evaluation, it's important not just to look at process evaluations, which in many ways is all you have available, so that's certainly appropriate that all three of you

looked at it that way.

But to think more about the underlying purpose of the program. When you said that the proportionate prescribers who are prescribing after the RiskMAP was a magnitude lower than the proportion before, to me that's a success, not a failure. And the answer isn't to decrease the burden. The answer –- again the whole purpose of the program, until we can predict who's at risk of a ischemic colitis, is to steer the drug away those people. The whole purpose of the program is to increase burdens in order to restrict the use to the people who are sickest.

The other very big difference among the different programs, and why the contrast is so useful is Lotronex is a symptomatic drug where that's not the case, for example, for Tysabri. And so the goal of the RiskMAP programs in the different situations are dramatically different as they should be.

DR. METZ: I suppose it probably won't come as a

surprise that we disagree a little bit about that, which is healthy. But we think we've got evidence to show that even when we've defined what we believe to be an appropriate population, that the program has created barriers to access there.

Because again, you know, the research, and it's not just our research, indicates that there are many, many more patients out there that are using our product. And again if you look at the physicians who have registered in the program, only half of those are prescribing. And that's –- you know, we're talking about 3500 to 4,000 prescribers. So some of that feels a little funny to me, and it's a bit difficult for me to think that there aren't more patients out there for who this therapy is appropriate. But again –-

DR. STROM: Again we obviously disagree, and my perspective is biased. I was on the Advisory Committee that heard the presentation twice about the committee.

And I think the key disagreement revolves around this question of appropriateness and who are the appropriate patients. That you're seeing appropriate patients as anybody who has the indication, and I'm seeing the appropriate patients as only those people who are so sick that they're willing to go through all of this grief to get access to the patients –- to the drug because we can't identify otherwise how to steer the drug away.

DR. METZ: But when we labeled it, the people that labeled it believed that that population was severity defined as we defined in the label was appropriate for treatment. Now clinical practice has taken it some place else and that's where we are right now.

DR. DALPAN: Okay. Yes, we'll just alternate sides.

MS. BLOOM: Good morning, Cheryl Bloom, MS patient. Dr. Bozic, thank you for addressing my comments yesterday about the unavailability of the patient

enrollment forms. I was actually just being facetious, but I knew why I couldn't have them, so it wasn't a problem, but thank you anyway.

Also the patients that asked about changing infusion sites will look forward to the simpler process. It is an issue and that's why I brought it up yesterday. And also I'd be happy to provide you with more information and work with you on any of the issues that I brought up yesterday, so please contact me or get in touch with me.

DR. BOZIC: Thank you very much. Thank you very much, Mrs. Bloom. I mean we do want to probe even more to understand the entire patient experience of the program from enrollment right through the infusion experience. So any help you can provide us on that would be very important to me. Yeah.

DR. DALPAN: Speak more closely into the microphone.

DR. BOZIC: Yeah. I was saying that we are very

interested in understanding a lot more about the patient's perception of the whole enrollment process and the infusion process. And any help you can provide us in this regard would be very helpful.

MS. BLOOM: Okay. I'd be more than happy to work with you on that.

DR. DALPAN: Okay, on this side of the room?

DR. PACE: Wilson Pace, University of Colorado and AFP. Three questions for Dr. Metz about Lotronex. And I think we want to move away from the concept of whether –- our own opinions about the drug and focus on the process because that's what we're here to talk about.

So you kept talking about experience of primary care, but as I heard your own data, you said that 76 percent of your prescriptions now come from gastroenterologists. That means you have less than 2,000 primary care physicians the entire country, which is less than 2 percent of all primary care physicians in the

country that are using this drug. I want to know whether you have any data prior to your RiskMAP program about how many primary care physicians were using it.

Secondly, I'm interested in whether you've done a geo-mapping of people who get your drug and see how that maps out to where they live. And thirdly, I'm interested in the sticker program. We had one before for other drugs as well. The IOM from (indiscernible) Medical Errors Committee indicated that we'd like to have all prescriptions written by electronic prescribing by 2010. We went a step further. We said they all should be transmitted electronically. We saw no reason that certain prescriptions should be on hard copy format. We think electronic prescriptions should be safer than putting them in hard format. How do we deal with stickers when we move to that?

DR. METZ: So in order, I think. Prior to product withdrawal, the balance of prescribers was tipped

towards primary care. And after product re-introduction, what you see is 76 percent of the prescribers being gastroenterologists. The primary care physicians, for whatever reason, have decided to stay home on that.

Yes, we did do –- again we were concerned about access, especially in areas of the Midwest or the west where prescriber density isn't quite –- certainly for the specialties, isn't very high. And right now, we have not seen any access issues that are related to regional distribution, but we have done those analyses.

Back to the sticker thing. The reason that we used the sticker, and it's a primitive tool, but we were dealing with a situation, you know, four or five years ago, was again to have some indication that that prescription was arising from this prescribing program for Lotronex. So if we can find a different way to do that, then that's fine, and we can put the sticker people out of business.

DR. PACE: Are there conversations going on with the MR manufacturers and the people who –- I mean basically most of the prescription writing packages are plug and play activities anyway. They're usually done by third party products. I was just wondering –- if those –- I guess my point is if those discussions aren't going on, they need to be.

DR. METZ: Yeah, and I guess I'll ask Dr. DalPan that because fortunately I only have one to worry about right now, and he gets to see them all. So the stickers, are they going to stay with us for a while, or do you see those going out of vogue?

DR. DALPAN: I think that the general experience with stickers is that they're probably not the best way to do things. I think we're all looking forward to better, more modern ways of doing things, you know. I hope in 10 years we're –- much sooner than that, we're still not talking about stickers. Yeah. Although to get in here on

Tuesday, you needed a special sticker, so we'll see. Okay, so, yes, sir.

MR. LILIENFELD: Yeah, David Lilienfeld, Fibergen. At many companies, the pharmaceutical marketing department isn't particularly renowned for being welcoming of interaction with drug safety or safety ideas, to put it mildly. However, in successful RiskMAP programs, such as you've presented, that obviously isn't the case. And so I'm wondering is there any suggestions of a carryover effect taking place within the marketing operation from those folks dealing with RiskMAP programs to other efforts that will perhaps be more balanced and which was the way in which various products are portrayed?

DR. BOZIC: I guess I can speak to that and say that our commercial organization has been not only totally supportive of the risk management plan, but they've actively embraced it. And I think like Dr. Freeman's comment, I think we have a company that's imbued with –-

or permeated with a sense of risk management. So everybody really thinks in terms of those terms. And yes, it has permeated to other products and how we approach drug safety in general.

So I would say in general, drug safety is very, very integrated in all phases of clinical development as well as marketed products. And I guess I can't stress the importance of the culture of risk management. It's permeated our entire organization, including the commercial organization.

MR. FREEMAN: One fact and one anecdote to help support my experience. Firstly the fact, when I joined Celgene, drug safety personnel accounted for 10 percent of the company's entire global workforce. To my experience, that isn't common. Secondly, my third day on the job, I found myself arguing with sales and marketing over the inclusion of an item in the package insert. Unusually they wanted to put it in and I didn't. That also is

atypical in my experience.

DR. METZ: We have a –- one of our key commercial people was on the team that helped to develop the risk management program. They went to the FDA meetings with us. So they were a partner to that. And I guess I'd have to say, you know, we get it as an industry in general. Things are evolving. In our practice, it's a generative fairly comprehensive benefit risk management plan before we get proof of concept data on a drug. So I do see that getting embedded into the routine drug development activities now. And I think that's a good thing. I mean if you don't understand the need to manage risk, then you might not be in the wrong industry right now –- might not be in the right industry rather.

MR. LILIENFELD: Thank you.

DR. DALPAN: Okay, we're running out of time, but we still have three people at the microphone. So I'd really like to be able to get all three of them. And so,

Sidney, do you want to –-

MR. KAHN: Sidney Khan, Pharmaco-Vigilance Risk Management, Incorporated. Two brief questions I have. The first one goes to Drs. Bozic and Metz. And that relates to the application of these RiskMAPs in other jurisdictions. I mean the European Union, for example, does require RiskMAPs as well under E2E and Volume 9A. So the question is do you have similar or comparable RiskMAPs in Europe or not? And what has the results been there?

The second question goes to Mr. Freeman. And in relation to the success or the apparent success of the STEPS and Revlimid programs in preventing pregnancy, it would be very interesting to know what the population, demographics are that are currently being exposed to this drug because as we heard, if in fact in the population is really not of child-bearing age, then it seems like you’re spending a great deal of effort for potentially not very much result.

DR. DALPAN: Before you start, just mention that Dr. Lumpkin's going to be here this afternoon talking about EMEA and RiskMAPs. So we'll have more discussion on that topic.

DR. BOZIC: Okay. Well, I can speak specifically for Tysabri. So Tysabri is currently marketed in about 18 countries of the world. So in every country there is a risk management program.

So the EMEA's risk management program has some similarities and some differences with the U.S. program. So the similarity is that it's heavily weighted towards education and training. So there's a lot of outreach efforts. There's a lot of education, prescribers, and infusion nurses. The difference is that because of the way the regulations are set up in Europe, we don't have control distribution, and we don't have registration of all prescribers, patients and infusion centers. So it's a more education-based system rather than a performance

linked access system like the one we have in the U.S.

You know, in terms of the relative success of the programs, it's still very early days. And I think over time we'll really be able to compare the two programs from the ultimate outcome, which is really the health outcome's perspective, i.e., the incidents of PML and serious opportunistic infections, and the outcomes of those types of events. So this is something that we'll pay attention to very carefully over the next few years.

DR. METZ: I can be uncharacteristically brief in my response. Lotronex was never marketed anyplace outside of the U.S.

DR. FREEMAN: In terms of the question about how much effort the company is putting in versus the size of the at-risk population, I guess two comments. Firstly, our emphasis isn't only on females of child-bearing potential, of course. We're also focusing on males that account for I think about 50 percent of our treated

population. And even if the numbers of females of child-bearing potential are small, that in our view is more than enough justification of running a program like this.

DR. DALPAN: Okay, I'm told we have to stop at 10:20, so I'll use the clock most favorable to giving us the amount of time. Please keep your questions and comments and your answers as short as possible so we can get as many people in, please.

MS. BLACKWELL: Mary Blackwell, Boston University's School of Medicine and School of Public Health, and a patient with MS on Tysabri. I really –- this is really more for the policy people here. I think the very term RiskMAP obviously emphasizes risk. But I think we really need to think about the conceptual framework in terms of –- you know, health services research generally looks at promoting access to patients who need care. And the emphasis has clearly been on risk.

You know, the patient medication guide –- we

went over this yesterday –- but it says what do patients need to know about Tysabri. And it appears that all they need to know is that they might get PML and die. I was appalled by your statistic that only 77 percent of the patients on Tysabri appear to have any working knowledge of the benefit. And I think that is, you know, the –- it's a benefit risk analysis as much as a risk benefit analysis.

So I really want, you know –- is it really a measure of success that you have fewer people on the drug? You need to really know about the people who aren't on the drug and are they people who should be on the drug. And, you know, what are we doing to try to make sure that people who need the drug, or are appropriate for the drug, get it as much as the people who aren't on the drug –- or people who shouldn't be on the drug aren't on it, and that people who are on the drug are safe? This is a really high level conceptual framework question in terms of how

are we approaching this and making sure that not only do we limit risk but that we maximize benefit.

DR. DALPAN: Let me just take that by saying I think that's probably one of the big reasons we had this meeting was really to understand how all these little –- all these independent programs and these different methods of things fit into a larger conceptual framework that I think we do need to look at and re-examine as we move this forward. So I think the kinds of things you're talking about are the kinds of things that we have noted as well and have wanted to bring out in a public forum just to –- which is what we're doing today.

MS. BLACKWELL: But I think it's really concerning when there are actually a number of practitioners in this audience that, you know, their main impression of Tysabri is that it was pulled from the market. And therefore there's this –- well, it's probably bad.

DR. DALPAN: Again I think these are the kinds of things we wanted to hear about, and that we're going to use as we move forward.

MS. BLACKWELL: Right, I appreciate that.

DR. DALPAN: Yeah. Okay, one more here. Yeah.

MR. GANGNON: I noticed –- Jean Paul Gangnon with (indiscernible). I noticed that no one mentioned any interactions with payers, patient groups or –- there was a little with pharmacies. Did any of you have any interactions with these groups? I just wonder if you included them in developing the RiskMAPs for the products. And I wonder if –- especially the payers, influence the success of the RiskMAPs programs through their coverage decisions. I just wanted –- I noticed this –- you know, we had the payers talk yesterday, and yet you didn't even address them.

DR. BOZIC: So I just want to take that question. In developing the risk management plan, we did

seek very broad feedback from all the key stakeholders, you know, prescribers, patients, infusion nurses, as well as payers. So they were part of the development of the plan.

Having said that, despite the indication statement for Tysabri that allows both first line and second line use, many of the plans have required that patients fail at least one therapy before they can get on Tysabri. So they've introduced the notion of STEP therapy around Tysabri. And so that is an example of some limitations to access that we've experienced.

MR. FREEMAN: In terms of thalidomide, the various thalidomide victims groups worldwide have been heavily involved in the development of the STEPS and now RevAssist programs. I can't speak to the payer interactions.

DR. DALPAN: Okay, quickly, if we can do one last question then.

MS. SMITH: All right, thanks. Meredith Smith from Purdue. For Richard Metz, you had made a comment. I think I heard you correctly. Something about the need for real world experience implementing some risk minimization actions or interventions. And something –- comment about imbedding them in Phase III studies. Could you elaborate and maybe give an example?

DR. METZ: In a Phase III program, either in the context of your primary efficacy studies or as –- in a parallel study as was discussed yesterday. But again you're aware of your pharmacology hopefully by the time you get into Phase III. And you might be well aware of what an expression of exaggerated pharmacology might look like. So are there some key messages that you can build around that that might make their way into product labeling, into a medication guide, or patient information leaflet. And can you do some independent research with patient focus groups and model those messages and see if

they understand the message, if they can comprehend that. And if they would take action, if action is indicated.

And the same for the prescribers. Do you understand what the pharmacology is here, and the things that you need to be on the lookout for and patients who would not be appropriate for therapy? And again if you can get a product off to a good start, it's going to be a lot easier to keep it in the marketplace, even as things evolve as they do. But when something gets off to a bad start, very difficult to chase that train down the tracks.

MS. SMITH: Thanks.

DR. DALPAN: Okay. Thank you all, and thanks to our speakers, our panelists. And we'll take a break now, and Ann, do you want to give some instructions?

DR. TRONTELL: Thank you. We'll start the open public hearing at 10:35. We had one of our speakers withdraw. Ask you to be back at that time. And I'd like to invite the speakers to come to the front of the room

and we'll discuss the procedure and your presentations.

(Break.)

DR. TRONTELL: Thank you all. We're about to open, have the open public session for those individuals who registered to speak. May I ask the participants in the back of the room if they need to continue their conversations to take them outside of the room, please?

We have –- each of our speakers is going to be speaking for five minutes. We have as our first registered Gary Slatko from Paragon RX.

MR. SLATKO: Good morning. My name's Gary Slatko. I'm the chief medical officer for Paragon RX. We're a company that designs RiskMAPs and other benefit risk communication programs. I'd like to talk to you today briefly about three methods or action steps that we can all take to achieve, improve RiskMAP performance after we leave this meeting.

The first step is to design our RiskMAPs more

rigorously using methodologies like failure mode and effects analysis and others that are available to us but have not been applied very routinely during RiskMAP program design. The second is to use tools that have been innovated and are in practical use by clinicians today, since clinicians are partly in the business of managing risk themselves. And thirdly to measure using continuous quality improvement principles.

In terms of improving RiskMAP design with greater rigor, I share with you a little vignette. We were asked to give a second opinion on a RiskMAP program that contained 30 tools that were brainstormed by an experienced consultant. We applied the failure mode and effects analysis methodology to those 30 tools. And what we found is that we could only utilize 17 of the 30 in the ultimate RiskMAP that was developed. And that there were another 11 tools that were frankly missing from the original design.

And what that led us to was a set of 28 tools which were a hybrid of the 30 original and the ones that were added that also included the benefit from systematic design of redundancy, the incorporation of adult learning principles, metrics and measurement systems, and a continuous quality improvement plan. We don't yet know the impact or effectiveness of this program as it's still being implemented.

But I think it's safe for us to say that brainstorming alone is an insufficient method for designing risk minimization action plans. And yet it's probably still the most pervasive way, along with precedent, that such programs are still designed today.

The second step to improving RiskMAP performance is depicted here. Improving implementation by using clinician innovators and clinician innovations in your RiskMAP design. Ineffective implementation marginalizes even a well designed RiskMAP. PhRMA manufacturers are not

likely to design care process interventions that are going to be accepted by many clinicians. In fact you're more likely to get the reaction, some of which has been alluded to of what were they thinking.

Clinician innovators are more likely to innovate practical risk reduction tools and systems that fit into their workflow and, hence, are going to fit into the workflow of other clinicians. To uncover these field tested tools and techniques, we suggest that you might want to observe how expert clinicians reduce risks in their own practices before you design your RiskMAP.

Here's an example of the difference. To address lab test reminders, a manufacturer might develop the things that we've seen and heard about over the last day, a package insert, a brochure for the patient and the physician, a website with product information and risk management information. It may even include an opt-in for patients to sign up so that if they get a call to be

reminded they have to go in and get their lab tested. And in some cases they would include a registry to confirm that the lab test result was documented before they were allowed to refill the prescription.

A clinician who is designing such a risk minimization action plan in their practice might design something like this. Doctor-signed prescriptions for a series of lab tests. The nurse counsels the patient to call the office for the test result. Hands the patient an information sheet and gives it to the caregiver as well. The nurse records the date on a lab test log that they implement in their practice. And the receptionist calls the patient, patients who do not call into the practice to find out the lab test result on time. And the question is rhetorical. Which one do you think other clinicians would likely implement?

Clinicians are in the business of innovating risk reduction tools and systems in their office practices

today. When they do, they consider things like patient flow, time and cost savings, patient satisfaction and compliance, who's going to be doing the work in the practice, what is a valued colleague or respected colleague done in their practice, the ever present avoiding night calls, and other risks besides just product safety that they're in the business of managing.

And what they produce are tools like these –- questionnaires, but in the waiting room so that it doesn't interrupt the office flow, counseling scripts, checklists that sit on top of the charts that reminds them what they need to do, log sheets, like I've just described, lab tickle systems, we've actually seen these tickle systems developed in various physician practices to make sure that they see the lab test results or know that it didn't come back, instructions for the caregivers, and others.

The third step to improving RiskMAP performance is improving measurement using continuous quality

improvement principles. The first version of the program is likely to under perform expectations. I think it's very important to keep that in mind. We've heard some examples earlier this morning of some significant efforts being made to make sure that evaluation takes place, assuming that the first version might not be successful.

You measure because you need to know what you're want to fix and what you want to leave alone in version 2.0 of the program. And the FDA's been very creative and constructive about how to go about doing this, establishing a goal and objectives, creating metrics and measurement systems, scheduling the evaluation and reporting of the results. And this information informs how we redesign RiskMAPs for better future performance.

So I'd like to conclude that what I'm suggesting here is really a three-step CQI, continuance quality improvement approach, to improving benefit risk. Very appropriate in this house of quality in our country.

Rigorous scientific risk assessment and design methods combined with clinician innovated tools to reduce risk and a plan to measure and improve RiskMAP performance. And I thank you for your time this morning.

DR. TRONTELL: The next speaker.

MS. KWEDER: Our next speaker is Luis Gutierrez from Covance, Incorporated.

MR. GUTIERREZ: Good morning. My name is Luis Gutierrez, and I lead the Commercialization Services group within Covance, which brings us comprehensive competencies to conducting clinical trials and risk management programs on a global scale. And as such, we are actively involved in a number of the programs that have been discussed at this meeting.

We fully embrace the concept of risk management across the full continuum of drug development. Gary brought that up earlier, which extends the real world use of a molecule. Development doesn’t end with an NDA. And

the knowledge base doesn’t end with the NDA.

My comments today will focus largely on RiskMAPs and the implementation of RiskMAP strategies. We have extensive experience in this, including the design and management of the iPLEDGE program, perhaps the largest and most complex program based on the metrics that were developed earlier of its type. That has led us to really, really value stakeholder feedback, and we certainly received our share.

It is incumbent on us regardless of our role here, the prescribers, the patients, the regulators, etcetera, to understand that patients and their healthcare professionals gain easily understandable information on both the benefits and the risks of (indiscernible) therapy so that they can make a truly informed treatment decision. In fact one of the key lessons we’ve learned is the paramount importance of thoroughly testing RiskMAP educational materials and procedures to ensure that they

actually are easily understandable and practical for all of the relevant stakeholders.

Once a RiskMAP program is operational, we must then also measure the overall effectiveness of the program in achieving its stated goal and incorporate the appropriate evaluation measures proactively, up front. The evaluation component of a RiskMAP needs to go into the design, not simply be an afterthought that gets tacked on later.

We've spent a fair bit of time at this meeting talking about the need to balance risk and benefit in patient and provider materials. But we also need to be aware of balancing the benefit and the burden of the program itself so that we don't inadvertently or even advertently reduce access to patients who can benefit. Some of the presentations today showed that we end up with a skew. The population after doesn't necessarily look like the population as a whole as epidemiology would tell

us. Moreover it's critical to ensure that a robust testing cycle is conducted to assess and then minimize the unnecessary burden experienced by their stakeholders.

Optimally risk management is an iterative process that is integrated. And it begins with in vitro testing, the very earliest part of drug development as Dr. Strom showed us yesterday, and continues throughout the entire life cycle of clinical trial testing and through post-market approval. The goal at every one of those stages, however, is the same –- scientific characterization of the product safety and efficacy profiles, recognizing that the tools necessary to make that characterization change over time and with evolving use.

Looking at some of the practical considerations for implementing risk management program components, it's important to note that risk management planning and implementation is by no means a rigid and sequential

process. It would be great standardized, but I think that they will –- these programs will reflect the diversity of the risks in the patient populations going forward. I don’t think there’s a simple cookie-cutter solution.

In closing, a comprehensive risk management program must be designed to simultaneously and proactively address patient safety, satisfy regulatory requirements, and establish a full understanding of the products risk of benefit profile. Within such a program is a strategic safety plan designed to decrease the product risk by using one or more interventions or tools that extend beyond the package insert and routine post-marketing surveillance.

It is essential to note that the effective implementation and evaluation of a RiskMAP is a complex and multi-faceted undertaking. These are not easy to do. Our experience has taught us that it involves ongoing, continuous engagement with numerous stakeholders, development of a complex and integrated information

systems so that you can answer the questions that arise as the program evolves, development and data management approaches, astute sensitivity to privacy concerns –- initially that hasn't actually yet come up at the session today –- and then close attention to the regulatory reporting requirements. But first and foremost –- and I think it came up throughout –- is an uncompromising focus on patient safety, the Hippocratic oath of first do no harm. So thank you very much for your time.

DR. TRONTELL: Okay. Thank you for your comments. Our next speaker will be Aparna Mohan from Johnson & Johnson Pharmaceuticals.

MS. MOHAN: Yes. Aparna Mohan, and I'm the director of epidemiology in the Benefit Risk Management group with Johnson & Johnson. I would like to share some of the key lessons that we have learned in the process of preparing and implementing risk management action plans for the opiate products.

We have found that surveillance plan is key to monitoring the RiskMAP effectiveness, and that an effective surveillance plan should maximize the information on identified risks, possibly warranting the use of multiple data sources. And when multiple data sources are used, one has to consider how the data will be retrieved in a coordinated manner, how the conclusions in the recommendations will be documented, and how the company will provide a coordinated and responsive action to an identified signal.

And now let’s go through each of these points in some degree of detail. Measuring RMP effectiveness using a surveillance plan. Usually we use target measures to evaluate the effectiveness of a RiskMAP. For example, the effectiveness of a physician education program which may be in place to address the issue of off label use may be measured by physician comprehension surveys after the educational campaign. The survey does not measure the

effect of the educational program on the actual risk, which is the off label use. However, a well thought out surveillance plan will be able to assess the effectiveness of the risk minimization tools by directly measuring the risk. For example, is there a change in off label use before and after the implementation of such an educational campaign.

The use of surveillance, or the purpose of a surveillance blend goes beyond just monitoring the risk. The surveillance plan must be able to measure changes in risk which may be a direct measure of the effectiveness of a RiskMAP. And in order for this to be a successful measure of effectiveness, the surveillance blend must be designed around the identified risks and the tools in place to minimize the risks. For example, for our opiate risk management plans, it was necessary to improve the quality and the nature of the information collected on the adverse events of interest. And we did –- we accomplished

this mainly by having standardized intake groups at the call center.

It’s also important to translate the risks into measurable terms. And in order to do that, we reinforce the already existing practices, growing practices, for the ease of interest, and we provided standardized query forms for subsequent retrieval of the adverse events of interest. And at the end, we need to understand that we have to look at the data over time, trend analysis of the adverse events of interest. Trend analysis of the usage pattern or prescribing pattern is valuable as a direct marker for the success of the risk management plan.

The routine surveillance database may not be able to address all the identified risks, which might necessitate the need to look at other data sources. So it is important to research all possible data sources with its ability to capture all the adverse events of interest, its limitations, its advantages, and to provide this

information in a timely manner.

For example, in preparing the risk management plan for opiate products, we had to look at a number of databases which is outlined in this diagram. It included medical claims databases, electronic medical records, and a number of publicly available data sources. And at the end, we selected the following databases, including our internal J&J post-marketing database, the FDA errors database, and a number of other data sources.

And you have to understand that a single data source may not be able to capture the information on all the adverse events of interest necessitating the use of multiple data sources. And we selected these databases based on its ability to provide data on a timely manner, data on the ease of interest, and information on a brand level basis.

Some of the other data sources that were considered, including the medical claims database and the

electronic medical records, had its own limitations, including under coating and the cash payments and street drug use not being able to be captured, which is important for opiate products.

DR. TRONTELL: Would you please conclude?

MS. MOHAN: Sure. So in conclusion, surrogate measures are usually employed to evaluate effectiveness of a RiskMAP. And an effective surveillance plan is key to monitoring the RiskMAP effectiveness, and it provides a direct measure of its effect, which might necessitate the use of multiple data sources to capture all the information of interest. Thank you.

MS. KWEDER: Thank you very much for your comments. I hope we will have some additional discussion of some of those same topics. Our next speaker is Pam Dixon from the World Privacy Forum.

MS. DIXON: Hello. I'm Pam Dixon at the World Privacy Forum. We're a non-profit public interest

research group based in California. We focus on long-term and in-depth research of policy and privacy issues. So I have some difficult things to say today. And I want you to know that I say them with the best intent and in the spirit of helpfulness. So with that as my backdrop, I'm going to begin.

So first off, thank you for the opportunity to testify and to talk about this. The FDA has not paid attention to privacy standards that are applied to RiskMAPs in the settings. Unfortunately this lack of attention has resulted in inappropriate and frankly unethical marketing practices that are applied to patients within some of these RiskMAPs. The FDA needs to set privacy standards that are applied for all RiskMAPs evenly that will resolve this problem.

The marketing use of patient information that is collected for the safety and public health and research purposes is an unsupportable practice that should be

expressly prohibited by the FDA, if not by statute. Privacy protections that are advanced for patients from the marketing uses of their sensitive information that is input into RiskMAP situations will actually help public health and ensure that patients are more compliant as opposed to less compliant. There's no need for privacy to interfere with the goals of RiskMAP programs.

To cite just one example, which is we did an analysis of the iPLEDGE program and that RiskMAP, and we found systemic privacy issues. However, by far the most significant and most troubling issue was the use of the marketing of sensitive patient information that was gathered for treatment purposes as all of you here know. That patients who prescribe the drug, isotretinoin, either Accutane or its generics, are enrolled in a computer-based program. A lot of very sensitive information is collected.

The FDA was quite aware that there could be

marketing issues in this program. In a hearing last year actually, they actually asked a question during the iPLEDGE discussion. They said my question is will these data by the manufacturers be used for any purposes other than pregnancy prevention or detection efforts. Because in the past, we asked would they be used for marketing or any other use. The reply was to your last question, absolutely not. The data is only for risk management purposes. This was February 10th of 2006. However, this statement directly contravenes the iPLEDGE privacy policy, which states –- by the way, this was from today –- "we provide the information in iPLEDGE to trusted partners who work on our behalf or with iPLEDGE under confidentiality agreements. These companies may use your personal information to help iPLEDGE communicate with you about offers from iPLEDGE and our marketing partners. However, these companies do not have any independent right to share this information. Further, iPLEDGE may combine

information about you that we have with information we obtain from business partners or other companies." And it goes on. And there are many, many loopholes in this privacy policy.

I have to say if this activity were to be conducted under HIPAA covered entity, this would be expressly illegal. In the state of California which has CMIA, which is the Confidentiality of Medical Information Act, it probably is currently illegal. So I think that just because RiskMAPs are not under the statute of HIPAA does not mean that they should not be protected from HIPAA covered ideas and values.

The World Privacy Forum appreciates the FDA's efforts to make drugs available and safe. But the FDA has not done enough to set standards for privacy practices in RiskMAPs. iPLEDGE is but one example of a RiskMAP. Other RiskMAPs have even more opaque practices. We were not even able to obtain the privacy practices for any other

RiskMAP. They may be available, but we weren't able to find them. There may not even be privacy policies for the other RiskMAPs, which leaves patients completely unprotected from any practice that these RiskMAPs can get to them.

The FDA must immediately attend to this issue in such standards that will apply to all RiskMAPs. Whatever the standards the FDA determines, one of them should be to expressly prohibit marketing to patients who have disclosed information for treatment purposes in a RiskMAP setting. Thank you very much.

DR. TRONTELL: Our next registered speaker was Lynn Goldman from Johns Hopkins. We haven't had her register. I'd like to give her a minute to identify herself if she's in the room. Then if not, I think we'll -- so then our next presenter will be Li-Ling Liu from the Department of Health in Taiwan.

MS. YU: Good morning, everybody. I'm working

in the Bureau of Pharmaceutical Affairs, Department of Health in Taiwan. It's my pleasure to have this chance to share experience with you in Taiwan.

First point I'd like to share with you is that we have an economic tool to control the compliance, and it's known as (indiscernible) practitioners for field which is their requirement. Then the drug can get reimbursed from our national health insurance. So in Taiwan, our pharmacists play a very important role in order to get reimbursement from our national health insurance.

The second point I'd like to share with you is that when we do the RiskMAP, we needed to think about that. The RiskMAP may inference the product access. It might increase the (indiscernible) product such as the (indiscernible). The teenager might not be ready to go to see the OBGYN doctor and sign the patient consent form. They would rather purchase the product from an illegal

place. That's very dangerous for their health. So when we do the RiskMAP, we need to pay more attention to the (indiscernible), and to pay more attention to the public education. Thank you.

MS. KWEDER: Thank you very much. Our next presenter is Calvin Knowlton from Excelerex, Incorporated.

DR. TRONTELL: This is another individual who didn't come forward. If you're not present, we'll go on to the next speaker, Joseph Cranston from the American Medical Association.

MR. CRANSTON: Good morning. My name is Joseph Cranston. I'm director of Science, Research and Technology at the American Medical Association. And I'm pleased to present these comments at this workshop on behalf of the AMA.

The AMA shares the common goal with AHRQ, FDA and other stakeholders to optimize the benefit risk balance of drug therapy. Improving the safe use of

prescription drugs after they are marketed is a primary means to achieve this goal. In that regard, the AMA supports a broader, more robust and better funded post-market surveillance system to improve drug quality. Since 2002, the AMA has provided detailed comments on RiskMAPs, the FDA, the Congress and the IOM's Committee on Drug Safety.

My goal today is to highlight six key points from these various communications. My first point is that the AMA strongly agrees with the FDA that the FDA approved professional labeling or package insert should be the routine risk minimization plan for the vast majority of drug and biological products. Recent changes in the format and content of the package insert, particularly the addition of a highlight section, should make the information more useful and user friendly to physicians.

My second point is that the AMA supports improved risk communication to physicians as the preferred

risk minimization plan for most drugs that require a risk management beyond just the package insert. There clearly is a need to identify and implement more effective strategies to communicate drug safety problems to physicians.

In prior communications to the FDA, the AMA has suggested some possible ways to improve risk communication. I'll not discuss them today for time constraints. However, I will mention that the AMA recently convened a meeting between the FDA and 11 high prescribing medical specialty societies. The goal of that meeting was to identify the most promising ways that the FDA and specialty societies individually or collectively could move forward in a collaborative manner to improve risk communication about drugs between the FDA and practicing physicians. We believe some promising ideas came out of that meeting, and the AMA looks forward to continuing this collaboration.

My third point is that the AMA continues to recommend that higher level risk minimization plans, such performance linked access systems and summary (indiscernible) systems be used only as a last resort to keep high risk products with unique and important benefits on the market.

I want to emphasize that the AMA is not opposed to all such RiskMAPs. In fact, we worked closely with Roche Laboratories many years ago in designing the very first Accutane risk management program. However, the AMA believes that if these more intrusive risk management tools are expanded to more pharmaceutical products, the potential for unintended consequences is significant. These include reduced patient access to necessary drugs, use of alternative drugs that may be less effective but a lower risk, and reduced manufacturer investment in innovative but high risk drugs. That said, we make the following recommendations when such high level RiskMAPs

are indeed necessary.

My fourth point and perhaps the most important message I'll deliver today is that the FDA and pharmaceutical companies should seek the input of practicing physicians when planning higher level RiskMAPs. This will give assurance to physicians that a RiskMAP is being developed based on good science, that the minimum number and least intrusive RiskMAP tools are used, and that the plan will be feasible and acceptable in usual physician practices. This may be best accomplished by working directly through medical specialty societies whose members are most likely to prescribe the drug being considered for the RiskMAP.

My fifth point relates to the development of specific RiskMAPs. In addition to including practicing physicians in the process, the AMA has recommended that RiskMAP tools be selected based on evidence of their effectiveness in achieving the specified objective. The

minimum number of tools should be employed, and the dual goals of minimizing the drug's risk and maintaining the widest possible access to the product. While the decision to develop a RiskMAP needs to be determined on a case-by-case basis, every effort should be made to use a standard set of tools for drugs with similar types of risks.

My last point is that the AMA strongly supports the need for rigorous evaluation of both RiskMAP programs and individual RiskMAP tools for their effectiveness. Drug sponsors should select well defined evidence-based and objective performance measures in determining whether a particular RiskMAP program is achieving its objectives. In addition, each RiskMAP tool employed in a specific program should be evaluated periodically as part of the program to ensure it is contributing to the achievements of the program's objectives. Ineffective tools should be eliminated. FDA should establish and maintain a public domain website that includes the available information on

the effectiveness of specific RiskMAP tools and programs. Thank you very much.

MS. KWEDER: Thank you very much. Our next speaker is Janet Phoenix, International Research Center for Women and Families.

MS. PHOENIX: Good morning. I'm Dr. Janet Phoenix. I'm director of Policy Research for the National Research Center for Women and Families. We're a think-tank focusing on health issues pertaining to women and families. And we've done a lot of work on Food and Drug Administration issues over the years.

The first comment I'd like to make is that we're very comfortable with many of the aspects of the RiskMAP process for medications where it's clear that there are known special risks. What we're less comfortable with is what we see as a need for improvement and in recognizing that all drugs have risks which need to be minimized and that we need to do a better job of communicating those

risks to the public.

In particular, we're concerned that information about clinical trials were not made available to the public so that they have all the information that they need to make informed decisions about what risks actually exist for drugs which are approved. And we've advocated that through efforts to improve current drug safety legislation that's currently being considered in Congress, that these discussions and negotiations between industry and the agency be made public, and groups such as ourselves or other groups who are acting in the interest of patients and consumers be allowed to participate in the process.

It's a concern of our's that we feel the post-market surveillance process needs to be greatly improved. And that there needs to be a better balance within the agency so that more attention is paid after drugs are approved, and that we can do a much better job of

monitoring safety. And improving the surveillance system looking at more active methods of surveillance so that we have adequate information about adverse events earlier.

We've worked a lot on focusing attention on the conflict of interests, which we see as a pervasive problem in the Advisory Committee process. And we studied over an 11-year period the Advisory Committee process and wrote a report pointing out what we see as an egregious issue that people sitting on it –- some people sitting on advisory committees have distinct ties to industries whose drugs are being considered for approval, and we take issue with that.

We also would like to see better balance in composition of the committee so that as we're evaluating the information we receive about whether drugs are safe or effective, that we have expertise in areas such as bio-statistics, other areas to improve the ability of the committees to really assess the information and improve

drugs so that we don't send the wrong message to the public that just because a drug has been approved, that it really is safe. And I think that's what the public assumes.

Direct to consumer advertising is not the best way to communicate information about risks to the public. And direct to consumer advertising that starts immediately after a drug has been approved is a travesty, and exposes large populations to unknown risks before we've had an opportunity to see what the safety profile of an approved drug actually is. So we're not in favor of that. We also feel that direct to consumer advertising encourages larger use and use of medications that may be more appropriate for smaller populations of patients. And so it's a problem we think.

In conclusion, some aspects of RiskMAPs we think are appropriate to ensure that the consumer is protected from known harmful effects. But we're concerned that for

many approved drugs, information about harmful effects is not shared with the public at the time that it becomes known. This can cause an unsuspecting public to take medications, assuming that approved means safe and sets us up for disasters like Vioxx or Ketec. Thank you.

DR. TRONTELL: Thank you. Our next speaker is Richard Gliklich from Outcome.

DR. GLIKLICH: Thank you. Thank you for the opportunity to speak today. My name is Richard Gliklich. I'm a physician, and I'm president of Outcome Sciences, which does businesses outcomes, a provider of patient registries and RiskMAP programs, and also one of the 13 AHRQ decide centers that were described yesterday.

Outcome has developed and managed several reminder and performance linked access systems, including one of the clozapine PLA systems. And I also recently served as the principle investigator for developing the AHRQ's handbook, "Registries for Evaluating Patient

Outcomes, A User's Guide." Based on those experiences, I'd like to share some thoughts on some of the comments that we've heard over the last two days, in particular on an area that we haven't heard a lot about yet on how healthcare information technology could be used to improve RiskMAPs. And as a corollary, what future actions AHRQ and the FDA should consider.

As we move into the era of more personalized medicines where a goal of therapy is the right drug for the right patient at the right time, and our ability to detect the right patient and the right time, improves through more specific diagnostics and more clear predictors, an increasing risk of harm over benefit. Reminder and PLA system RiskMAPs will become a critical part of the delivery of more and more healthcare products.

Although these systems have demonstrated success in limiting distribution when properly implemented, these systems are closed solutions that are not integrated into

the mainstream of healthcare technology. And that some implementations result in significant provider and patient burden as we've heard. For example, reminder systems are those that prompt, remind, double-check or otherwise guide healthcare practitioners in prescribing, dispensing, receiving or using products in ways that minimize risk. The current guidance document on RiskMAPs, which is what this is taken from, describes a wide range of potential programs from patient education to provider training, to stickers, and from paper to electronic, without a hierarchy or situational recommendation based on supporting evidence of relative effectiveness.

Performance-linked access systems provide product access by limiting prescribing or dispensing to certified providers or to patients with documentation of safe use conditions. As we have heard, PLA systems are generally more effective than other approaches in preventing harm. But they sometimes do so with the cost

of loss of access to the very life saving or life improvement therapies that they're intending to help safely distribution. However, this is not universally true, but we don't know when it's really universally –- when it's true and when it's not true because there are anecdotes but very little scientific literature to suggest why some programs succeed while others fail.

From a systems perspective, we view PLA reminder and PLA system RiskMAPs as a continuum of increasing while those of information or controls to multiple actors at different points in the cycle of prescribing, distributing, dispensing and receiving drugs. Clearly health information technologies offer great promise for managing complex data driven decisions. However, it would be short-sighted to assume that the mere inclusion of electronic reminder systems, some of which we heard about yesterday at the point of prescription, for example, will be a panacea.

The initial data in 1998 from Bates Leap and colleagues and computerized physician order entry systems on avoidance of adverse events was dramatic. But it really was not very long before Damakus, Et Al reported (indiscernible) on the phenomenon of alert fatigue. That the benefits of such systems appear to deteriorate over time. With a large number of personalized medicines in clinical development, a more comprehensive and standardized model that addresses all of the touch points and in multiple situations and in multiple ways needs to be designed and now is the time.

We respectfully offer the following recommendations for your consideration. First, we believe that as you have heard, the healthcare information technology can have a significant impact on the effective delivery of reminder and PLA system RiskMAPs. This can include not only reminders and authorizations, but performance feedback for providers, links to needs-based

education for providers and patients and other capabilities. But this needs to be orchestrated in a manner that can accommodate large numbers of personalized medicines with more and more data points needed to identify, distribute and in some cases, continuously evaluate safe responders.

In other words, the scalable technology model needs to be established that will utilize disparate health information systems rather than generating new redundant systems each time a new RiskMAP is required. Such a model may use web and voice systems which have proven to be effective particularly in our pre-health information technology world. But they are siloed, and most importantly, they'll increasingly need to utilize existing health information systems to collect and distribute information. With uniform standards for receiving and sending data, this is achievable.

At the same time, the processing for each

RiskMAP should be done centrally by specialized scalable and undate-able systems. This centralization is necessary for two reasons. RiskMAP algorithms can be computationally complex, changing, and often require information from multiple sources as well as having multiple recipients as we heard yesterday. Further, patients do not necessarily stay within the same health system. By creating a technology model based on open and defined standards, any number of reminder PLA systems can work simultaneously through the web, EHR's, E-prescribing systems and pharmacy dispensing systems in a way that would be vendor neutral. In other words by establishing a model and interchange standards for health information technology world, the health information technology world will be pre-wired, if you will, for RiskMAPs.

Furthermore, by utilizing this open standards approach, not only will the burden of new RiskMAPs be lessened on the providers, but the incremental costs of

these programs will decrease through efficiencies and competition. Based on Outcome Science's experience with programs that already utilize this open standards approach for patient registries to what a term web service is, we're confident that this is achievable.

DR. TRONTELL: Can I ask you to conclude, please?

DR. GLIKLICH: Finally I suggest a couple of goals for AHRQ and the FDA towards developing collaboratives to improve definitions of risk and to fine tune the conceptual framework for RiskMAPs, to evaluate relative effectiveness as we've heard, and to consider a demonstration project towards establishing an open standards RiskMAP technology model. Thank you.

MS. KWEDER: Okay, thank you very much. And I believe our last speaker for today is Doris Hare from the American Foundation of Maternal and Child Health.

MS. HARE: As a member of the National Institute

of Health Data Monitoring Committee for the Obstetric Pharmacology Research unit, I thank you for holding this meeting.

Two of the risk minimization tools discussed at this meeting are education and outreach intended to inform patients about the products, intended to –- excuse me –- intended to inform patients about the product's risk and reminder systems to guide patients and healthcare providers in using a product in ways that minimize risk. The FDA's approved label, which the public tends to refer to as the package insert, is one of these tools.

In light of the fact that many pharmaceutical companies have removed their labels from the PDR, it is essential that the package inserts of all FDA approved drugs should be made easily available on the Internet.

I'm concerned that the FDA has watered down the package inserts for many of the obstetric drugs. Until recently one could tell whether or not a drug had been

specifically approved by the FDA for obstetric use by looking at the indication section of the label, a section near the front of the label. If obstetric use was not mentioned in that section of the label, then the drug's use for obstetrics was identified as off label.

Now the FDA is approving labeling that drops the reference in the indication section and allows reference to a drug's use as a recognized use in labor and delivery. The use of that term is misleading because it obscures the difference between off label use and an FDA approved use. That watered down language appears in both the latest marcaine label and the label of bupivacaine, the generic form of marcaine.

The FDA has approved marcaine and its generic for the use of obstetrics, even though it is classified by the FDA as a Category C drug, which the Category C drug is interpreted –- let's see, risk cannot be ruled out. Adequate well controlled human studies are lacking. And

animal studies have shown a risk to the fetus and are lacking as well. That part of the sentence doesn't make any sense. There's a chance of fetal harm if the drug is administered during pregnancy. But the potential benefits may outweigh the potential risk.

In November of 2000, the Science Board of the FDA invited me to present my concerns regarding the FDA. And members of the Science Board did not challenge a single statement that I made during my presentation, nor during the months while they reviewed the accuracy of my concerns. I shall submit that presentation with the docket of this meeting.

My concerns are nothing new. In 1975, the FDA document entitled, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children," was prepared by the American Academy of Pediatrics Committee on Fetus and Newborns. That document acknowledged that drugs trapped in the infant's brain at birth have the

potential for adversely affecting the rapidly developing nerve circuitry of the brain and central nervous system by altering the role of maturation, sole migration, endritic arborization, cell differentiation, and mylonization. Now the work of Zhang, Heinz, et al, reaffirm that the migration of neurons along the gleofibers within the brain can be altered by changing the normal chemistry of the rapidly developing brain.

The FDA knows and we know that none of the drugs used in obstetric care has been subjected to a properly controlled scientific study and found to be safe for the fetus, exposed to the drugs in utero. In fact, the FDA has no written standards that must be met by pharmaceutical companies seeking approval for their products to be used in obstetrics. The only honest way to deal with the subject is to tell the reader there are no well controlled, long-term follow-up studies on individuals who are exposed in utero to the drug, to the

effect of this drug. There may be delayed long-term effects on the subsequent physical, neurologic and mental development of the exposed offspring that cannot be determined at this time.

Why if the FDA is charged with protecting the public from drug induced injury does the agency place the adverse effects of obstetric drugs so far along in the package insert that the information is very likely to be missed by the reader? If there are inherent or known risk to the fetus, why does the FDA not see the need for a black box of these risks and move them to the beginning of the package insert so that there's no chance that those risks will be missed by the physician or other healthcare provider involved in the mother's care?

Our high infant mortality rate is only part of our problem. We are 30th in a list of 30 countries. That's available from the World Health Organization. Our high –- let's see –- millions of children in the United

States are suffering from neurologic disorders, such as autism, dyslexia, schizophrenia, and many other neurologic disorders. And the list grows larger each day. American families are becoming impatient with an FDA that yields to the pressure of industry that dumb-down the information in the package inserts for obstetric related drugs. As pharmaceutical makers of obstetric drugs methodically as I said removed their labels from the package –- from the PDR, we have no other source of knowing, letting a woman know what the risks are.

So it is my hope that the combination –- I mean the two agencies that are working to further protect the American public will do their best to see that women understand that there are risks to obstetric drugs, and that they should at least minimize those risks, even if they have to have the drug. Thank you.

MS. KWEDER: Thank you, Ms. Hare.

DR. TRONTELL: Presuming that neither Lynn

Goldman nor Calvin Knowlton are here, this will conclude the open public session. Those of you who have comments in response to these or on any other matters at this meeting are invited and reminded of the open public comments that can come to the docket, and that information is available on the website.

We're about to embark on another Rockville lunchtime adventure. Today it's my understanding that the gates will not be raised but will be operating on an honor system. If you are sadly leaving us at lunchtime today, we ask you to return your key card and to pay on your exit. However, if you do plan to return, just simply let the guard know as you exit at the Gaither Road exit and you won't be charged, but retain your cards so that you can be appropriately charged at the end of the day.

We will resume at 1 o'clock. We have remaining sessions dealing with evaluations, some future options, including health information technology and a wrap-up by

our own Hugh Tilson. That's worth the price of admission right there.

(Lunch.)

(On the record - 1:00 p.m.)

DR. TRONTELL: Welcome back. As we're making ourselves comfortable, I also have one lost and found item I would like to ask individuals if they found a blackberry pearl, to let Lee Lemley know. We have an individual who's missing one.

I also want to ask the speakers, in particular the people from the open public hearing if they're still present, if you are willing to have your slides shared, to please see Lee Lemley and sign a waiver so that they may be posted to FDA's Internet site. And again, our expectation is that many of these slides will appear within the next several days.

We're now about to start Panel 5. I'd like to introduce its chair, Dr. Parivash Nourjah, a very

respected epidemiologist who's worked at the CDC and FDA in the area of drug safety and who works now at ARHQ. She's particularly strong in the areas of methodology and will be leading this panel on evaluation.

DR. NOURJAH: Thank you, Ann. Welcome to Panel 5, Evaluation Perspective. I guess I don't know how to go down. Do you know how to work with this?

(Pause.)

DR. NOURJAH: All right, sorry for that. Evaluation is a very important concept in RiskMAP program. Yesterday we heard that the main purpose of evaluation is to ensure whether the risk minimization program is achieving the desired goal and its objective. As today we heard in the morning and tomorrow we are going to –- in this session we are going to hear more about different purposes of evaluation.

In this panel we have four speakers. The first speaker is Dr. Anne Trontell. Dr. Trontell is a

pediatrician, an epidemiologist, who now directs the CERTS program at AHRQ. In her previous work at FDA, she chaired the writing of RiskMAP guidance and led FDA efforts in this area within the Office of Drug Safety.

The second speaker is Dr. Nancy Allen LaPointe. Dr. LaPointe is clinical associate professor at the School of Pharmacy, University of North Carolina at Chapel Hill. She's also associate professor in the Division of Clinical Pharmacy of Department of Medicine at Duke University Medical Center. She's the program director for Duke CERT. She's a member of –- a cardiology expert, Committee of U.S. Pharmacopia.

The third speaker is Dr. Brian Strom. Those of you who were here yesterday heard Dr. Strom. And for those of you who weren't here, Dr. Strom is a professor of bio-statistics and epidemiology, professor of medicine, professor of pharmacology at University of Pennsylvania School of Medicine.

And the last speaker is Dr. Judy Racoosin. Dr. Judy Racoosin has been working on pre- and post-marketing drug safety issues at FDA CEDA for ll years. Currently she's a senior safety policy advisor on the safety policy and communication of staff in CDER's Office of the Center Director.

Now these are my ground rules. Each panelist will present for about 15 minutes. Questions and comments should be made at the end of session. You need to come to the mikes, which are located at two locations. Please identify yourself and the panelists to whom the question is addressed. Thank you. And now I'm inviting the panelists to come to the table.

(Pause.)

DR. TRONTELL: Thank you, Parivash. I think the other panelists will watch the slides from the audience until their turn comes up.

The good news about talking to you about

evaluation at this point in the day after dealing with the Rockville scene and whatever good lunch you might have had is that you've actually heard a lot of the things I have to say this morning. So I hope actually to move relatively quickly in my slides and just hit some high points and perhaps reinforce some messages you've already heard.

I'm going to talk generally about the importance of evaluation already stressed, some of the challenges in measurement performance, some of the resources and how we would hope this information could be widely shared.

The purpose of evaluation is really to look at the impacts of RiskMAPs. And we know from the stakeholder groups that met this last day that RiskMAPs' impact are felt by many. These include the patients who take the drug, you know, the physicians who prescribe it, the pharmacists who dispense it, and the pharmaceutical and biologic industries that make it. However, there are

other stakeholders, some of them have been represented here today. These include the healthcare institutions that seek quality healthcare for their members, a growing number of government and private interests that not only pay for drugs but also recognize their associated healthcare savings or their potential healthcare costs if adverse events occur. And also a number of federal and state entities that regulate drugs, or perhaps the healthcare professions in settings of care that may have a voice in these programs.

But I would submit that these diverse stakeholder groups do share a common interest. It still is very patient centered. These conform very much to AHRQ's strategic goals which is to look and achieve medication use that is safe, effective, efficient and of high quality.

Now the question is how do we wrap our hands around those terms? Can we make them a little bit more

real? Well, safety and effectiveness is really looking to determine whether or not the benefits that are attained, either on an individual or a population base, in fact outweigh the harms that are incurred in the use of the medication.

Efficiency is a kind of a grab-bag term that can encompass a number of areas that might include whether or not appropriate access is maintained to the drug, or whether or not in fact healthcare participants or healthcare operations have minimal added impact in terms of costs or burdens in terms of their delivering healthcare, which is what this is all about.

And quality, again a more difficult term to absorb, encompasses safety, effectiveness and efficiency, but also looks very much at the health services environment to see whether it increases the likelihood of desired health outcomes being achieved. And also that it operates in consistency with current knowledge and

evidence based practice.

To drill down a little bit more in these areas, we look at what might be the measures. And very broadly when we're talking about safety and effectiveness, we're most comfortable talking about health outcomes. And RiskMAPs are often framed in terms of health outcomes to be avoided. If those cannot be directly measured, we seek the closest surrogate. It might be some, you know, intermediate end point or something else. We also must consider in safety and effectiveness, the potential unintended consequences. Sometimes we're lucky enough that those are beneficial, but sometimes they're adverse themselves and need to be folded into this equation.

For efficiency, we might look to see are there barriers encountered by any of the various members of the healthcare system and additional costs. And as we've heard some even from our public speakers, we might look very closely and sort of a continuous quality improvement

model at the processes that are engendered in the conduct of a RiskMAP program. Are people really carrying them out completely? Do they fit with what needs to be done in failure mode and effect analysis, or root cause analysis can be done if problems or areas of inefficiency might be identified?

And again quality reflects back upward on safety effectiveness and efficiency. But we might also look at some issues. Some are related to access of equity. Are people able to access this product? Are there barriers related to their socio-economic status? And is there some aspect of satisfaction or appropriateness in therapeutic decision-making that we might be able to look to?

One more step down, can we be even a little bit more concrete –- I'll confess to being highly conceptual in this talk –- to looking at actual target outcomes that we might look at for achieving health outcomes or close surrogates. You know, do we look to get a zero rate of an

adverse event? Or do we consider something else? Is 88 percent going to be the happy place for all of us to say that we've hit the mark?

We might also look toward the processes involved in a RiskMAP. In particular, the component, tools within a RiskMAP program to see if they have been adequately completed. They may in those instances where health outcome data are not available or where we may have a long lag time before we might expect to see the health outcome data, the process data, may be able to inform whether or not you're moving in the direction that you want. If you can't necessarily determine pregnancy outcomes, you may be able to look at positive pregnancy tests as an indicator of pregnancy exposure.

Other areas more nebulous relate to the quality or satisfaction with decision-making, again this begs the question who do we ask, who is to be satisfied, and what are the best and most appropriate instruments to assess

that. And really back to the fundamental issue of risk communication and education, what I've called on this slide knowledge transfer, it's can we look to see do people even have the necessary information to know how to operate, to know that a RiskMAP exists, to know its component parts, to know the reason for its existence, and to take the appropriate steps. How might we best assess this.

In the realm of RiskMAPs, we're almost inevitably working with observational data. Unlike randomized data, they're prone to a number of sources of a bias or error. We seek an observational data to get good outcome measures that would be validated to an accepted standard. So a code on an administrative claim or others we would hope would be well connected to an actual event that truly had occurred. And to do that with high sensitivity and specificity. We want in these measurements to look to populations that are free of

selection bias that have, you know, some representative nature of the population so that we're not picking either the most healthy or the sickest individuals in the capture methods that we use. And that also the populations over a size that we can really measure the effects we're interested in. And again issues of error, we've looked to avoid confounding by other associated factors that we hadn't considered or a possible misclassification.

And I think we heard this morning about issues with survey design. Surveys are a very attractive mechanism often proposed to FDA for purposes of evaluating a RiskMAP program. They have great strengths. They include the ability to augment the readily available administrative data and allow you to customize the data and to obtain diverse input. But surveys can be limited because the individuals who participate may not be representative. And surveys themselves are somewhat tricky. As some of the individuals in the audience know

they’re subject to framing effects and other important design issues. And we do run into the challenge which is when you’re asking people to report on their behavior, particularly if it’s sensitive, or there may be some perceived social desirability or undesirability to the outcome that they may be less inaccurate.

Many discussions around RiskMAPs get down to a final issue which is where are we aiming, what is the –- as the, you know, the term has become to be known, the metric that we’re seeking. Some of the challenge again is methodologic. How do we set a reference group or comparative? We heard this morning it’s 27 percent, 29 percent about as good as you’re ever going to get as a voluntary participation rate for a survey. Are we looking to the general population? Are we looking to those people who have the disease or the condition? And among those groups, will we look at the individuals who aren’t treated for our sort of baseline of what we might accept? Are we

looking to the individuals who are receiving alternative therapy in terms of their risk benefit profile? Ideally some kind of time series analysis looking at pre- and post-RiskMAP implementation would be a way to determine their effectiveness, but for those products that start their lives with a RiskMAP, we have the difficulty of knowing the right baseline.

The targets themselves may be a matter of intense debate. We've heard different numbers today. Although these goals are set to be expressed in terms of zero or a hundred percent, we have to ask about how realistic they are in terms of actual operations. And might we be able to describe incremental progress that would be acceptable. If not, the achievement of some absolute number. And again, that will still bring us back to a difficult question which is how much product risk and how fast should we expect to achieve it. Clearly these are important issues, and I invite your consideration of

who might best participate and how in making some of these decisions.

The timing of evaluation is not just at the end. Clearly there's a continuous element, and we've heard today from many organizations that are already implementing that kind of evaluation. But as has been heard, some assessment prior to the design of a RiskMAP program or as part of the design can help inform the process of what's the existing knowledge base, what are the processes that are already in place for delivering care in that particular setting, and how might tools be adapted and best assimilated into clinical practice.

Clearly periodically or continuously if possible, some examination of the program for its success and implementation from sort of a quality assurance process to see if individuals are in fact completing and doing what is done. Again this may help to identify those program components that are particularly critical for the

success of the RiskMAP, or perhaps even identify some that are redundant, duplicative or even actually deleterious to its effectiveness.

And clearly periodic assessment has to be agreed upon to assess the overall performance of the RiskMAP either for some absolute goal that we've agreed upon or some appropriate target progress rate. But the question again really relates to how frequently can this be done. And again how and who might best be involved in agreeing to that periodicity.

Evaluation is an area that draws heavily upon individuals in epidemiology and other observational science. These are individuals who are often in short supply. Industry and government has access and contains individuals with this expertise. And certainly academic and private entities themselves can offer this work. They're often funded by industry or government.

I think we've heard in this form many concerns

about openness and trust. And I think some of the aims in whoever is conducting evaluation is that their work be configured with transparency and to seek avoiding any conflicts real or even perceived in terms of the reporting of the success of a program.

And let me conclude by talking with the need and the value of sharing the results of evaluation. Again we've heard many requests and comments over the last day and a half to have some common place where we can have this information. But by evaluating these RiskMAP programs, I think it's how we might seek to inform and improve their performance. It's a really learned in a collective way what are some of the best practices that would improve effectiveness or even potentially allow us to establish some consistency in the tools that work well that people might pick from in a future menu of options so that we'd have less customization than we currently experience.

And it's part of the larger game of learning and knowing, of education. And again the term knowledge transfer hops up. FDA in its guidance spoke to its intention to work with its FDA Advisory Committees, in particular its Drug Safety and Risk Management Committee, to examine these plans. Or even to have a website where their performance is described. And certainly that would be something we would love to hear more about.

There's also scientific publications, the possibility of the professional guidelines might look to or incorporate these activities. AHRQ is in the process of developing an innovations clearinghouse where such results might –- good lessons learned might go. But I invite you to consider other opportunities how we all might collectively learn more to advance the science and practice of RiskMAP programs. Thank you.

MS. LAPOINTE: All right. It's always difficult doing a talk this time of day in what I call sort of the

post-lunch period where everybody's getting kind of groggy. I guess the good news, depending on your perspective, is that I tend to talk very rapidly, albeit not as rapidly as Dr. Tilson. However, hopefully fast enough that any slipup will evade his detection, and I won't end up on a slide at the end. So by way of disclosures, I just –- this is nowhere near I guess what you saw from Dr. Strom earlier today, or yesterday, but just wanted to make that –- make you aware of that.

What I've been asked to talk about today is the Dofetilide Risk Management program, and not the program, but evaluating that program. But I would be remiss if I didn't give you a little bit of background about what that risk management program looked like, and a little bit of the program to sort of set you up for when we talk about the evaluation.

It's hard to believe actually that this drug came on the market over seven years ago now, and so we

really did this evaluation, or started the evaluation over seven years ago, so it's been a while. It was a new anti-arrhythmic drug that was first marketed in the year 2000 for conversion of atrial fibrillation to sinus rhythm and also for maintenance of sinus rhythm. It was known at the time that it was being approved and brought to the market that it had a dose and concentration dependent risk of torsades de pointe which essentially is a potentially life-threatening cardiac arrhythmia.

In atrial fibrillation, the indication for this particular treatment is typically not a life-threatening disease. So basically you had a setup where you're bringing a drug to market that had a potentially fatal adverse effect and be used for an indication that wasn't necessarily a fatal life-threatening disease. Also I think it's important to note that during this time, there were several drugs that had been removed from the U.S. drug market because of QT prolongation and causing

torsades. So that was sort of the environment that this drug was coming out into.

So just very quickly, the key elements –- and I'm not going to go through all of the components of it, but the key elements were that patients who were being started on dofetilide had to be hospitalized for the initiation of the dofetilide therapy. The second key component was that there was a mandatory education program, and you've heard that a lot with a lot of the RiskMAPs. And actually at the time I don't think the term RiskMAP even existed. We called these things risk management programs at the time. But there was a mandatory education program, and that was for really anybody who essentially had anything to do with a dofetilide patient. So it was the nurses, the pharmacists, the physicians, even the EKG technicians if they were monitoring telemetry had to go through an educational program before the hospital was able to

certify that they could get the drug into their hospital to begin giving patients dofetilide.

And that really led to the development then of a database of prescribers. So if a prescriber completed the educational program, their name went into this database, and then, thus, they would be allowed to prescribe dofetilide.

Also you've heard several descriptions of restricted drug distribution program. And this one had it as well. And as I mentioned, I sort of alluded to the restrictions on just the hospitals getting the drug in-house. But also for patients, there was restrictions initially where patients were only able to obtain dofetilide from a single mail order source. Now over the years and after we had completed our evaluation, that had been expanded to where pharmacies could actually have their pharmacists undergo the educational program and then be allowed to bring the drug into their pharmacy and

dispense it to patients. But just keep in mind that that all happened after the evaluation that I'm about to talk to you about.

And then I would say the fourth key element was really there was a very specific dosing and monitoring recommendations or guidelines set up for dofetilide down to what dose to use based on a patient's renal function, when to check EKG's, how frequently to check EKG's, how long someone should be in the hospital. So very specific dosing and monitoring recommendations.

So in thinking about how to evaluate this particular program, there are several challenges, and I underline some. There's many more than what I've got here, but these were some of the things we were thinking about in terms of how to set up an evaluation of this particular risk management program. The first is that torsades de pointe, this adverse effect that we were worried about, is relatively uncommon. And it is very

difficult to retrospectively identify in claims data because there's no ICD-9 code for it, etcetera. So it's difficult to sort of get your hand around how frequently this adverse effect occurs out in the real world practice.

QT prolongation also does not always led to torsades de pointe. So even though you may look for QT prolongation, that doesn't necessarily mean that the person who has QT prolongation would have gone on to have torsades. So it may be a less than perfect surrogate marker.

So some of the key questions were how should success or failure of the program be defined, what level of risk was acceptable, and what is the role of potential surrogate endpoints. And a couple of them that we considered and actually ended up using in our evaluation was first looking at adherence to those labeled instructions, those dosing and monitoring instructions. And then also assessing practitioner acceptance of the

program.

So basically it was a three-pronged approach in evaluating the program. I think it's important to note two things. First, this risk management program was in place at the time the drug was first marketed. So there was never a period of time where dofetilide was freely available, and then later the risk management program was added on. It was in place from the get-go.

The second key piece to this is that there really to my knowledge was no plan to do any sort of formalized evaluation of the risk management program when this risk management program and the drug came on the market.

And so what we did is we tried to think of what are some things that we can do to try to get a handle on whether or not this risk management program is working. And you can define working in a lot of different ways. So the three-pronged approach was first, we wanted to assess

practitioner perceptions. This was the first time really a cardiovascular drug had come to market with a risk management program. And we were curious as to what the response of the practitioners would be. Obviously if they thought that the program was burdensome or problematic in any way, they likely wouldn't use the drug and that'd pretty much be the end of that. So we thought we –- first key thing is we wanted to assess their perceptions, and we did that in our institution only.

And then the second was looking at prescriber acceptance. And by that, I really mean use of the drug. So how frequently was the drug used, not only in our institution, but we also got some data to look nationally at prescriptions for dofetilide.

And the third was looking at adherence to the labeled dosing and monitoring guidelines. And I think that it's also interesting that at the time that dofetilide came to market in spring of 2000, the FDA had

also approved the use of another anti-arrhythmic drug called Beta Pace AF, which was sort of a new formulation of a drug that was already on the market. And that one was now indicated for this particular formulation for treating atrial fibrillation. It was also a drug that had a dose dependent risk of torsades de pointe, so there was a lot of similarities between Beta Pace AF and dofetilide. However, Beta Pace AF did not have a risk management program and the dofetilide did. So they were coming out on the market about the same time.

Now we can get into the discussion later about some of the other differences or nuances to that, but we thought it was a unique opportunity to really kind of compare what was happening to these two drugs as they were coming on the market.

So first, the practitioner survey. We surveyed all practitioners at Duke who had completed the educational program essentially to get their opinions of

the overall program, the dosing and monitoring guidelines. We also assessed the time required for the hospital to implement the program. And we also did a mini-quiz, and I'll explain to you later as to exactly what the mini-quiz was.

So first, some results. And this is from the survey, and this was some of the questions that we asked practitioners about the educational program itself. And this is based on a five point Likert scale, five being strongly agree, and one being strongly disagree. And what I have here are the means plus standard deviations listed.

And so you'll see –- I'm just going to point a couple of things out that overall when we asked them if they thought the risk management program was necessary, there was a tendency toward agreement that they thought it was a necessary program for this particular drug. However, interestingly, if you look at the bottom one, we asked them if they thought dofetilide was potentially more

dangerous than any other anti-arrhythmic drug, and there was a tendency to disagree with that. So it appeared as though they did not think that dofetilide was necessarily any more dangerous than any other anti-arrhythmic drug that they used. However, they thought that it was –- the risk management program was reasonable.

Then when we asked them questions about the guidelines, it was interesting that they felt overall that the guidelines were sort of mediocre in terms of understanding, more of a tendency to not think they were so easy to implement. But they did seem to agree that you should check QT intervals, that your patient should be hospitalized, etcetera. But they also said they were less likely to use dofetilide off label than they were other anti-arrhythmic drugs. And that may be related directly to the fact that it was more difficult with the risk management program.

So then the mini-quiz was essentially trying to

assess their recollection of a couple of the key points in the educational program. And you have to keep in mind that most of the practitioners took this quiz shortly after they completed the educational program. So it was really short-term recollection. We didn't go back and ask them a month or a year later do you still remember these things. But for the most part, they seemed, especially physicians and pharmacists, seemed to have a pretty good understanding that dofetilide was contra-indicated in patients with severe renal insufficiency, and that they needed to check electro-cardiograms two to three hours after each dose.

When we asked them about medication errors though, we didn't get such a good response. Only about 25 percent of respondents were able to correctly identify all six of the drugs that were contra-indicated. When you look sort of at the mean number of how many they actually did get, it was closer to about 50 to 75 percent of the

drugs they were actually able to identify.

Okay, so in summary from the survey, it appeared that there was general agreement that the program was necessary. But they didn't think dofetilide was necessarily more dangerous. There was less agreement that there recommendations were easy to understand or implement. And interestingly, it took our institution about 145 hours just to prepare to bring dofetilide into the hospital, and that does not account for the about one hour per practitioner that was required to complete the educational module. So if you add that in, you have a pretty significant investment in time within a hospital in order to implement this risk management program.

Okay, then moving on to use or acceptance, these are the numbers from –- actually in our hospital, it took us a fair amount of time to get through this educational program, even though the drug came on the market in the spring of 2000. It really wasn't until about the fourth

quarter of 2000 that we were actually starting to bring our first patients in. And these are actual numbers. So we're talking less than 10 patients in the first quarter up to about a year, a little over a year later in the first quarter of 2002 that we were only looking at about 23 patients. So very, very, relatively small number of patients.

Nationally this wasn't a lot different. I know this is hard to see, but I think you'll get the jest. The top line is basically total number of new and refilled prescriptions for anti-arrhythmic drugs in the United States from April of 2000 through December of 2001. And the line that's sort of turquoise that's hugging the zero is the dofetilide line. So it really did not make much of a blip on the radar screen at all. And in fact, if you break this down even more and look at sort of a comparison between dofetilide and the Beta Pace AF, you'll see that the Beta Pace AF, which was marketed about this same time,

took off more rapidly, albeit not tremendous, but wasn't used more frequently than the dofetilide.

Now what you're not seeing here, though, is that Beta Ace AF already had –- there was another sotalol product on the market that was used much more commonly. And in this light it's actually kind of hard to see, but the yellow line here is the overall sotalol use. So sotalol was used quite frequently, and this is now only in atrial fibrillation patients. The dofetilide again is the turquoise line that's very much hugging the bottom and barely making a blip on the radar screen.

Okay. So it really didn't appear that over the time period that we were looking at, prescriptions for dofetilide that much has really happened. There were not a lot of patients getting this. The third piece of our evaluation was then looking at the adherence, the dosing and monitoring recommendations. And so we looked at all the patients with a pharmacy order for dofetilide or

sotalol over a one year period of time and then did chart abstractions on all the dofetilide patients, but actually there were quite a few of the sotalol patients, so we limited it to a random 50 percent of those patients and did the chart abstraction.

I think it's important as you look at these results to keep in mind that we actually did something, sort of a step beyond what the risk management program required. We found that it was very difficult, or we didn't feel comfortable that our physicians and our practitioners would be able to keep track of everything that they needed to do in terms of checking EKG's, checking labs, those sorts of things. So we developed a standardized order set that was implemented at Duke at the time that this was brought out. Now at that time, we didn't have the computerized physician order entry, so this was a paper-based system. But since we've gone now to a computerized system, we've just translated it into

the computerized system. So it's actually still in place today.

And so here are our results. We had 47 patients during the one-year period of time on dofetilide, and then 50 percent of our sotalol was patients who were 117. And you'll see in terms of selecting the correct starting dose, we had 79 percent of the dofetilide versus 35 percent of the sotalol patients. And also the dofetilide patients tended –- they did a better job in terms –- or the physicians did a better job in terms of ordering the baseline ECG, the ECG's after first and subsequent dose, than was done for the sotalol patients. But interestingly if you looked at patients who actually were contra-indicated to receiving the drug, because of their QT prolongation at time of initiation, there was actually no statistically significant difference, although you'll see number-wise there was some difference.

Then again similar ordering baseline

electrolytes. Much better in the dofetilide group than the sotalol group. And interestingly when we looked at adverse events, the medication was –- it was an equal proportion of patients who stopped or the medication was held for an adverse event between the two groups. We had no cases of torsades de pointe in our sample from either group.

Ninety-four percent of the dofetilide prescriptions were written by an approved physician, so someone who was in the database. It's a little difficult to try to figure out why we had physicians who actually got –- still were able to prescribe the drug that were not in the database, but that's for another discussion. And then there were no interacting medications that were actually used at the same time with dofetilide.

So in summary, a couple of points. First, in looking from the perceptions of the program, overall I would say that the program was pretty well received. But

now I think the key point was that this was done before we actually started the first patient on dofetilide, we did this survey. So we assessed their perceptions before the program really started for the most part. And we never did do a follow-up survey after they had had some experience and had gone through the process to see if their perceptions had changed. So this was basically their perception of it going into the program.

The second point here is based on the little use of dofetilide locally and nationally, the question does come to mind as to whether or not ultimately people really felt that the program might have been too burdensome. Within our health system, we have three hospitals. And initially one of the three actually even chose to go through and bring the drug in house. So do all that education, training to be actually be able to use the drug. Ultimately the other two came on board, but it was years later.

So the question is about unintended consequences related to the fact that in this situation, you have several drugs that are available to treat or manage patients with atrial fibrillation, one of which has a risk management program and very well may have led people to not select that drug when they had other options available to them, but didn’t require so much work to actually get them to start the patient. I think the difficult issue here is that we do know that many of the other alternatives have the same risk as dofetilide did, yet were we in fact by putting the risk management program in place kind of leading them to using one of the other drugs, and they didn’t have the same level of education or understanding about what they were doing.

And then the third point here is that based on our study, there did appear to be better adherence to the dosing and monitoring guidelines as compared to sotalol, which indicated success. But I can’t really tell you

whether or not the success was because of the risk management program itself or actually the standardized order set that we implemented in hospital which is not a standard part of it and might not have been used by other hospitals. So I think that from our evaluation, from our perspective, we really can't sort that out. And I would guess that a lot of it had to do with the standardized order set rather than the educational program and having the physicians remember what they're supposed to do. Okay. And that's all I have. Thank you.

DR. NOURJAH: Thank you, Dr. LaPointe. And Dr. Strom.

DR. STROM: Thank you. I'm going to shift gears a little bit here and talk about a demonstration which is not actually a RiskMAP. But an experience we had in our institution, which I think has very direct implications though to thinking about RiskMAPs. So for those who weren't here yesterday, I'll briefly review background and

our drug use and effects program at our hospital. And then talk about how warfarin trimethoprim/sulfa with oxasole, TMS, study that we have underway or had underway. And it really has three major implications I think to the kind of things we're talking about in these two days.

One of them is the issue of IT and implications relating to use of IT in this way. We've heard IT mentioned multiple times in the last day and a half as a panacea. The second is focusing –- emphasizing again the need for evaluation that you can't assume anything necessarily works or works as you expect. And the third is raising some ethical implications that haven't much been raised but really need to be discussed in the context of evaluations of RiskMAPs.

So first I'll begin with my conflict of interest disclosure, becoming infamous now. Again as we talked about yesterday, very quickly, the iatrogenic injuries are very common. I won't read through this. These are

figures from the IOM. And whether you believe these figures or it's half as much, the point is it's a big issue. And adverse drug events are the most common iatrogenic cause of patient injury by far.

As an attempt to address that within our health system –- and again I mentioned this briefly yesterday –- we have had underway since the mid-1980's now our drug use and effects program which really has three key parts, our adverse drug reaction reporting program, our drug use evaluation program, and pharmacy use containment. The adverse drug evaluation program obviously collects adverse reactions, and I showed you a little bit of data there yesterday. What I'm going to focus on today is something emerging as part of our drug use evaluation program.

We have multiple different selected interventions under (indiscernible) as part of our drug use evaluation program where we look to try to change the way physicians prescribe drugs within our health system.

And again we have the advantage of a controlled health system, limited number of docs, all of whom are employees within the health system. Our private community docs are different. But the goal is to try to rationalize the use of drugs in the health system. So the goal is to avoid this, I stopped taking the medicine because I prefer the original disease to the side effects.

We've had increasing use of IT interventions. I mentioned these yesterday. Different warnings we've sent out using our electronic medical records system. And when we try interventions –- unfortunately the axis didn't reproduce –- let me, without the axis, let me tell you what's going in the wrong direction. This was use of metoclopramide within our health system. When cisapride came off the market, what we found is increasing use of metoclopramide and particularly increasing use of metoclopramide for long periods of time in high risk patients with the risk of tartidediscomesia associated

with that and the fact the number of cases of tartidediscomesia associated with that. And so we had multiple interventions to try to reduce the use. The horizontal axis here is time. The vertical axis here is utilization, and as you can see, it's going the wrong way. So rather than use decreasing, it increased. And so in that context and in a number of other contexts we've put in place multiple IT based interventions. But being an academic center and because it's the way I think, they're all done with evaluations as part of it. So I want to go through with you in a little bit more detail is the last one of these, the one on warfarin and trimethoprim sulfa.

The objective of this study is to determine if a computerized stop order will reduce the number of concurrent trimethoprim and warfarin orders accepted through the inpatient ordering system. As background, warfarin is obviously a common anti –- oral coagulant used for DVT, HO fib, (indiscernible) card valves and so on.

Commonly causes bleeding. The literature values talk about rates of major bleed that is causing death or hospitalization on the order –- ballpark of 5 percent a year. So this is not a small problem.

Trimethoprim sulfa is a very commonly used antibiotic, well known to interact with warfarin. It's probably one of the few interactions that have actually been shown clinically as opposed to just pharmaco-kinetically and accepted that there's interaction. And there's rarely an infection that is sensitive to only one antibiotic that you couldn't use a different antibiotic instead.

So we've had ongoing a very aggressive program in our pharmacy intervention program where whenever there's a concurrent order for warfarin and trimethoprim sulfa, the pharmacist calls the doc and says you didn't really want to do that, intervening to try to stop orders for trimethoprim sulfa order concurrently with warfarin.

Despite that, 186 inpatients received concurrent trimethoprim sulfa and warfarin during one recent year despite this very intensive intervention. The answer they inevitably got back is that's okay. I know. I'll monitor them. I'll watch them. And they watched them as they bled. And so this is not something you can fool yourself into thinking that watching is enough.

And so the other thing we found is because of the issue in IT systems of warning fatigue, alert fatigue as we've talked about a number of times, most of the warnings, which are basically a flag goes up and you just blow right by them are completely ignored. And we have very nice elegant data demonstrating the very large number of warnings we send out every day to every physician in the hospital that are completely ignored. And so we wanted to put in place not a soft stop but a hard stop, and to try to test the hard stop to see how that would work.

So our hypothesis was that an automatic stop order against simultaneous electronic orders for trimethoprim sulfa and warfarin would reduce the number of patients receiving both drugs concurrently compared to current practice. And again the goal was for an almost hard stop. We didn't feel a complete hard stop was appropriate ethically.

Design was a randomized clinical trial. The setting was our health system hospitals. Subjects were really the residents and nurse practitioners using the computerized prescription order entry system recall here that really when you're studying ordering, the real subjects are not the patients. The real subjects are the docs. But it obviously has impact on patients as well. But randomization was by doc. And so physicians are randomly allocated to get one version or the other. The primary endpoint was new concurrent prescription orders for trimethoprim sulfa and warfarin accepted through the

electronic order system. The intervention was an automatic electronic stop of the trimethoprim sulfa or warfarin order, whichever it was that was coming up.

And it was a pop-up window that didn't just pop up and then disappear or be able to click a button and make disappear. But it notified the physician or nurse practitioner that the order cannot be processed due to a significant potential drug interaction. That same pop-up window listed exceptions permitting for the processing of the order. So there was for ethical reasons an out whereby they could choose one of these very few exceptions. And if you chose one of those very few exceptions, then you could still have the order received. But that was not the default. The default was the order was stopped. And they had to overtly move forward to choose on of the exceptions and lie medically saying the patient had a disease they didn't have in the order in order to get past this. So the goal was for a hard stop

but a hard stop that was ethical. The controls were usual care.

As a study, and one of the things we need to discuss, is the issue of IRB approvals and studies. We submitted it to the IRB for approval. And ironically the IRB had troubles with the study. They were worried about random allocation to usual care. They thought it as unethical for us to randomly assign people not to get it because it was so clear this had to work that it wasn't appropriate to assign people to usual care. We tried to explain to them that's what we've been doing. But they thought usual –- yeah, that was not okay. This IT stuff has to work. And so they had a lot of concern about that.

The other issue was that because we weren't getting informed consent, that you couldn't very well get informed consent of the subjects who were the docs, this needed a consent waiver. And so the compromise solution was a sort of DSMB, reviewing each episode where the

system triggered an alert. Now this made a lot of work. Every time there is an alert triggered, that ended up getting over-ridden or not, that had to be manually retrospectively reviewed and reviewed with the oversight board. I used DSMB in quotations because it's not a DSMB. It's an –- as they've corrected me, it's really an oversight board. It works sort of like a DSMB, but the difference is that it's charted by the IRB, not by the investigator or the sponsor. It was advisory only, advisory to the IRB, not to the sponsor or the investigator. And they don't explicitly have the right to stop the study. They're advisory to the IRB, however, who can stop the study.

They also have no access to proprietary data or to data that are blinded, unlike most DSMB's. So it's different than the normal DSMB. But that was the compromise that we would do that with this study. We would do that with all of these studies, and we also were

going to send out and did send out an e-mail then and to every –- once a year thereafter to all of our prescribers in the hospital letting them know we are doing such studies and they may be the subject of such studies. And so we proceeded with the study. We thought it was a lot of work for very little benefit. It seemed like completely bureaucratic overhead, but we kept Atterby happy so we agreed to do it. However, to our shock, the DSMB did stop the study early due to episodes of patient harm in the intervention group. Remember they almost didn't allow this study because they thought it was unethical not to get the intervention. But in fact there were people who ended up needing the drug whose access to the drug was delayed by 24 hours because the doc didn't use the exception to the order correctly. The hard stop was too hard a stop. And no one actually got hurt, but the care was delayed for these patients and the study was stopped early because of that. So if we had this DSMB,

and if we had not done it as a randomized trial, we would have put in place in fact routinely an intervention that in fact the IRB considered unethical for us not to have. And in fact ultimately the intervention was stopped early because it was doing harm.

So conclusions are to my data, right or wrong, you don't want that. This is not the goal of what we're doing as a science based agency and a science based individuals. All interventions need evaluation to be sure they're effective and safe. We can't assume that is the case no matter how obvious it may be. And I would argue the same is true in RiskMAPs as well as the same kind of ethical issues arising in their evaluation. Thank you.

DR. NOURJAH: Our last speaker is Dr. Racoosin.

DR. RACOOSIN: Thank you. So based on my affiliation, you might be wondering why I'm here talking about clozapine. Until about a year ago for nine years, I was on the safety team and the Division of Neuro-

Pharmacological Products in the Office of New Drugs at FDA. And I spent much of those nine years working on the clozapine projects. So here I am today to talk about that.

I want to mention one of the points that Dr. Trontell raised about points of evaluation, or time points of evaluation, this program was put into place I guess –- maybe I'll refer to it as the granddaddy of RiskMAPs because if RiskMAP wasn't around in 2000 when dofetilide was approved, it certainly wasn't around in 1990 when the clozapine white blood cell monitoring program was launched. But the issue with the evaluation points that I'm going to talk about today were in many ways driven by the patient population who were taking clozapine and their family members. You know, when we talk about a burden to patients, a weekly blood test was felt to be burdensome. And given the benefit that they were getting from the drug, wanted to see if there were ways to minimize that

burden. And really in many ways that drove the two evaluations that have been done to date.

I'm going to briefly talk about the definitions of what we're talking about with agranulocytosis and moderate and severe leukopenia, give you some background to this program, and then talk about the two evaluation points that we had for (indiscernible) 1997 and then in June of 2003. And ultimately some labeling changes that came in the spring of 2005.

So these are the definitions here, and really it's just to put into context a couple of things. Moderate leukopenia is sort of the first sign that someone is getting into trouble with their neutrophils. Severe leukopenia is an even larger decrement and agranulocytosis as defined in the clozapine white blood cell monitoring program is an absolute neutrophil count of 500, but clinical symptoms are not required. And so it is a somewhat different definition than some may associate with

agranulocytosis.

Now agranulocytosis associated with clozapine have been identified in the clinical development program and it occurred in about 1 to 2 percent of patients. There was an advisory committee meeting back in 1984 that reviewed the clozapine efficacy trials, and there was a big concern about the agran at that point. And that's when it was decided that a study for clozapine needed to be done and treatment resistant –- in patients with schizophrenia who were found to be treatment resistant. So by history, they had to have failed standard therapy and then actually in the trial, they were randomized to a standard therapy. And if they failed, then could be randomized to clozapine.

And also in that time, the drug was available in Europe. And there was post-marketing surveillance data that showed that the agran associated with clozapine treatment had a high fatality rate of about one third.

And so when it was shown that clozapine was effective in treating patients with treatment resistance schizophrenia, there was a strong feeling that the drug could only be approved if it was made available through a distribution system that ensured a weekly white blood cell monitoring test, the so-called no blood, no drug rule.

Now Sandoz, who was Sandoz then, Novartis now, their original conception of the white blood cell monitoring program at the February, 1990 product launch was called the clozaril patient management system. And in that program, Caremark was the exclusive distributor and provider of weekly blood collection services. And Roche Labs analyzed the blood samples for white blood cell count. The data on the white blood cell counts and agranulocytosis occurrences were collected in the clozaril national registry. And patients who developed severe leukopenia or agran were listed on a non-rechallengeable list. So what had been noted is that patients who

developed severe leukopenia or agran if they were rechallenged with clozapine or at a high risk for redeveloping the problem and having increased morbidity and mortality. And so it was identified that patients who developed this severe leukopenia or agran one time should absolutely not be rechallenged. And so there was maintain this list.

I should note that because of the very sick population of patients who responded to clozapine, it was felt that if patients got down to moderate leukopenia and had the drug stopped and then recovered, should be given another opportunity to be rechallenged. And this practice in this country is distinct from what goes on in the U.K. where patients hitting moderate leukopenia are not allowed to be rechallenged.

Now the VA and various pharmacy groups and other stakeholders complained to FDA about the expense of clozapine only being available as being part of this

clozaril patient management system. Sandoz was sued by 35 State Attorney Generals for anti-trust violations. And in May of 1991, this CPMS was converted from its original conception into a non-exclusive distribution program. And there was a settlement associated with that lawsuit. Subsequently generic versions of clozapine have become available. That was in December of 1997, the first became available. And those generic versions are required to have a very similar white blood cell monitoring program to the innovator. Now each of those generic companies maintain their own database with white blood cell counts. But there's one centralized non-rechallengeable list, and that's maintained by Novartis.

So the first point at which we evaluated the need for weekly white blood cell monitoring came in July of 1997 when we took it to the Psycho-Pharmacologic Drugs Advisory Committee meeting. And the question that we posed at that time was on the slide. Should the frequency

of white blood cell monitoring be reduced at some time point after initiation of therapy? And if so, when and what reduced frequency of white blood cell monitoring would be acceptable? Should it stop all together, and if so, when? Or should the program be changed overall? For example, should it become voluntary?

Now we worked with Novartis. They did analyses of the data. They also provided the white blood cell data to the division, and we did analyses as well. This slide shows that the peak risk of agran actually comes to around three to four months into therapy and then rapidly drops off. And the range of what's seen after one year is in the same range as other marketed drugs that do not have monitoring systems, or they may have some recommendations and labeling, but no sort of risk management plan or just restricted distribution.

And based on the data I just showed and the subsequent discussion, the recommendation of that PDAC was

to allow a decrease in monitoring to every two weeks after six months of weekly monitoring as long as the white blood cell counts were stable. And this change in the monitoring program was initiated April 1st of 1998.

Now after that change was made, there was subsequent interest to see if after some period of every two week monitoring could the frequency be decreased even further. And so that was –- and that's generally what the question was –- brought back to the committee in June of 2003. There was an additional issue that came up because in our review of this data, we also looked at some data from the U.K. and from Australia. And in the U.K., they had a separate criteria for moderate leukopenia, which was that you could have a normal white blood cell count but be shown to have moderate –- basically agranulocytopenia based on just your absolute neutrophil count. So the question was, should we add a separate criteria of the absolute neutrophil count. So you could have an abnormal

or a low ANC that qualified you as having being in the moderate leukopenia range, still having a normal white blood cell count. So that was the second question.

And one of the things that was unexpected was that at the time of the 1997 Advisory Committee, Novartis had done a lot of work to try and project what would the severe leukopenia and agran rates increase to if we went to a less frequent monitoring. And so it was very unexpected when –- what we saw is that here for –- and we've actually –- this is broken out into zero to 18 weeks and 19 to 52 weeks so that it could be comparable to the U.K. and Australia data because those are the cuts that they used.

But what we weren't expecting is to see this unusual secular trend where in the U.S., just based on those first 18 weeks of weekly monitoring, that the agran rate would have been halved in this post-1998 period. And the clozaril national registry is really intended for

white blood cell monitoring. There's not a lot more data that is captured other than sort of an identifying number and the white count. So we really didn't have the ability to kind of delve in and figure out, you know, are somehow physicians practicing differently. Do they recognize that if someone's white blood cell count is starting to drop, that they're going to behave differently. We really don't know why that was. So that was a little bit mysterious.

But at the same time as –- what we were really interested in is this experience that the Australians and that the U.K. had with this monthly monitoring and how much could we expect to see an increase in agran should we go from the every two weeks ad infinitum to every two weeks for some period of time and then monthly ad infinitum. And so the U.K. had sort of the most relevant data, having had the every two weeks and then switching to monthly. And you can see that the rate of agran increased by about two times with that change. And the Australians

had always had monthly monitoring after the first 18 weeks. And so their rate of .5 cases per thousand patient years was very similar to what was seen in the U.K. And so we felt like we had a pretty good idea of where we would be headed.

The recommendation of that 2003 PDAC meeting was to recommend after some period of monitoring of two weeks that patients could decrease their monitoring frequency to monthly. That change was recommended only for patients who had had normal white blood cell counts through that time. And they recognized that this change might result in an increase in the agran rate. They felt that the program should not be stopped, and they did not think it should be made voluntary. And they also recommended that we go ahead and add the absolute neutrophil count as a independent criteria for moderate leukopenia.

And this slide just has sort of more of the labeling language around that change. And it added to –-

there was already a white blood cell criteria for starting clozapine and added in absolute neutrophil count criteria to that.

Now there was some other issues that were raised at the time that we held that 2003 Advisory Committee meeting that required us to kind of go back to the data and retrench, particularly for the population of patients who had one episode of moderate leukopenia. We were concerned that those patients had a different risk of going on to agran than patients who had sailed through there for six months of weekly monitoring and then second six months of every other week monitoring without a problem that these patients were different.

And when we went back to look at that population, there were seven to 15 percent of patients. And you know, there's some ranges here because of the way that –- there were different cohorts created based on the generics were added in. So I'm not going to get into all

that detail. But there are some ranges here, especially there's different risks associated with the first six months compared to post six months.

So in general about seven to 15 percent of patients had a subsequent episode of granulopoiesis dysfunction following their initial episode of moderate leukopenia. And of patients who had at least one episode of moderate leukopenia had a rate of subsequent of agran that was about three to 10 times higher than the full cohort.

And this next slide shows that patients who had two or more episodes of moderate leukopenia were at a much higher –- had a much higher rate of agran than those who did not have two or more episodes. It didn't seem to increase with every episode, but it definitely increased. And that increase risk persisted for about one year following recovery from the original episode of moderate leukopenia. And so we adjusted labeling for this group of

patients. So we added cautionary language to prescribers that described the increase risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia. And that increase caution translated into the requirements that patients who recover from an episode of moderate leukopenia undergo weekly monitoring for 12 months if they're rechallenged as opposed to just –- normally it would be six months of weekly, and then six months of every other week. This group has to –- when they are in the recovery period have to be monitored weekly for 12 months.

The challenges that we saw at the time that these changes were made were really educating prescribers and patients about the changes in the white blood cell monitoring program and assessing the effect of these changes on the agran rate, particularly because lessening the frequency of monitoring in long-term users may

increase the risk of agran and yet increasing the frequency of monitoring for patients who have had an initial episode of moderate leukopenia could potentially decrease the risk of agran.

And there's another complicating factor that I think has a lot of implications for RiskMAPs so they're going to continue over a long period of time. And that has to do with the addition of generics into the market. The analyses that we were able to do of the white blood cell counts that were collected in the clozapine national registry, we were able to do because Novartis had all the data. And in the analysis that was done for 2003, ultimately we ended up having to throw out some part of the data because when patients left the Novartis system and, you know, just go on to a generic , we did not have access to the white blood cell counts for those patients who left the system, so they were censored from the analysis.

So I think in a setting where you were sort of planning this in a more proactive way thinking about –- and we were encouraged at the 2003 Advisory Committee meeting to try and, you know, put –- somehow pull together –- get the registry pulled together for the various generics and the innovator. That effort at this point has not really been undertaken. But I think in an effort of a group who's planning this proactively, it'd be important to think proactively about when generics come into a –- you know, become available, how would the data from their monitoring system be linked up at least for the purposes of analysis. Now these things are linked for the purpose of patient safety such that patients, even if you develop –- or if you develop severe leukopenia or agran while on a generic, that is captured in all in one –- all on the same non-rechallengeable list. So regardless of where you go to get your clozapine, that list would be checked. And if you've had a problem, you're not going to get

rechallenged. But for the purposes of analysis, there isn't a shared registry.

A lot of work has gone into this over the years. And I just want to acknowledge a couple of my colleagues at FDA and formerly of FDA who have worked on this with me.

DR. NOURJAH: Thank you. Do you think if I asked my panelists to come to the table, they will come this time? And what do you think? Do you think I will learn how to work with this (indiscernible)? I doubt it. You can start.

MR. GLIKLICH: Okay. All right, my name is Richard Gliklich from Outcome. And my question is for Dr. Strom. I enjoyed your presentation, but one thing that -- the question's almost rhetoric in that as we've heard two presentations on evaluation strategies or several of them. But two of them were focused on single institution, academic, large academic centers. Could you just comment

on what you would suggest might be the best methodological approach to studying practitioner behavior more broadly, and whether that's using cluster designs and so on?

DR. STROM: Sure. A couple of comments. Assuming you're talking about evaluation of RiskMAPs in general as opposed to evaluation of interventions, obviously evaluation of interventions within an institution or in a controlled setting I think a cluster (indiscernible) like we did is probably the best way. You can't do that with evaluation of RiskMAPs because you're intervening on the entire population.

I think the way to see evaluation of RiskMAPs is as an inter-population based intervention. And then the study becomes an observational study. It's an observational study of whatever is already under way. And it's part of how you deal with the ethical issues accordingly. The intervention is not the study. The intervention is a public health intervention.

What you would actually do and how you would design it would really depend –- and again I'll come back to my hobbyhorse of the questions, what is the question. I think if you're looking at a (indiscernible) situation, your goal is to watch white blood cell counts, and to watch white blood cell counts come down. It was a very nice demonstration of the effectiveness of the program and how it was no longer needed after a certain amount of time. And then you re-evaluate and modify the program accordingly. There's a specific target and a specific outcome, and clearly to the degree you can follow that outcome, that's what you want to be able to focus.

If you're looking at an intervention program, a RiskMAP, where the goal is simply to reduce use to make it harder to use so you reduce –- so it only gets to the most severe patients, like Lotronex. I would argue that the best intervention is total sales, i.e., they should be low, and who they're used in. That is, they should be

used in the sickest patients. And then a series of process outcomes accordingly. So I think how you would evaluate –- I think each RiskMAP has to be tailored to the drug in question because the goals of the RiskMAP are different because the concerns are different. And the evaluation should be tailored to the objectives of the RiskMAP.

MR. GLIKLICH: Okay, and the use of single institution studies, would you recommend that or not recommend it?

DR. STROM: Oh, I don't think single institution studies are –- well, certainly what we were doing was not evaluating a RiskMAP. I think what Nancy was doing was or was anticipating a RiskMAP and can be useful, but certainly what you really want to do is be able to do national evaluations or national samples because the risks of generalizability of any single institution if possible.

MR. KAHN: Sidney Kahn, yet again. Two points

emerged from this last discussion. And I'd like to throw them to the panel and see what we can come up with. The first point I want to make is that the United States already has the world's most expensive healthcare by far. And the question I would ask is what would –- has anyone considered the cost benefit analysis of adopting these plans? You know, how much are we saving –- you know, how much is it costing us to save one adverse event, or, you know, what life over time? Because these are (indiscernible) that have to get made in many, many areas and not just in RiskMAPs, which we can talk about later. That's the first question.

But the other point I wanted to make also was that what struck me was the inconsistency that we encounter in these various RiskMAPs. For example, we heard about dofetilide versus amiodarone sotalol. Amiodarone's out there. It's at least as dangerous as dofetilide because it's not just (indiscernible), but it

also has a lot of other nasty adverse effects, but it has no RiskMAP. Similarly, the pregnancy warnings and the pregnancy contraceptive precautions for thalidomide and isotretinoin are not very dissimilar from those of a ribavirin, which does not have a RiskMAP. So the question I would ask you is what are we really trying to get at here? And are we just sort of looking under the lamppost because that's where the light is instead of looking over there where we actually dropped our keys in the shadows? So I'd ask that point. And if you really want to take this further, you know, ideally you should have a RiskMAP for metformin because everyone who gets metformin should have a (indiscernible) measured before they get to a point the (indiscernible) which can be fatal. And if you really want to go nuts, you can say whatever type –- you shouldn't be able to get a prescription refill for warfarin unless you present the results of an INR because that's a much more dangerous problem than, shall we say,

thalidomide. So I'll ask the panel to comment on that.

DR. STROM: I can begin if you want. Hopefully others will chime in as well. A few comments. One is I think a regulatory body should not practice medicine. And so a lot of the decisions you're talking about are issues that are details in the practice of medicine, getting INR's and warfarin and so on. You can't get into that on a global population basis. The regulatory decisions need to be made –- and the whole philosophy of RiskMAPs are these are drugs that –- whose risk benefit wouldn't be warranted were it not for these extra precautions that are put in place. You can't tolerate a thalidomide on the market if you can have birth defects associated with it. You wouldn't have a drug without it. By having the STEPS program in place, it allows society to have that drug.

From that perspective, I think your question of old versus new drugs, I'll leave for the regulators to answer. I mean clearly you're right that there are old

drugs that maybe should be subjected to the same kinds of regulations that new drugs get. That's not a new problem and that's not unique to RiskMAPs. Obviously regulation changes over time, and new drugs get stuck with the benefit of the new rules.

As far as cost benefit analysis, my own sense is that's irrelevant. That cost is only relevant when benefit and safety is in hand. And again these are drugs and these should only be used in drugs where you wouldn't have the drug were it not for this plan. And so the RiskMAP is an inherent part of getting access to the drug. They should not be used lightly. They should not be used in every single drug.

MS. LAPOINTE: I just wanted to add to that I think that the question about where to draw the line with what drug gets a RiskMAP versus which doesn't is a very difficult question because, you know, I've heard many time people say you don't think about over the counter

medication such as aspirin. Look at, you know, now if you were to bring aspirin as a new drug onto the market, there would be probably some pretty serious concerns about that particular product, and are we really informing the population appropriately as to what the risks of that drug are. So I think that that's a difficult question. I don't have the answer for that.

With regards to the anti-arrhythmic drugs that you mentioned, I alluded to a little bit in my presentation the differences between the sotalol and the dofetilide. As you noticed that sotalol, this particular brand, the Beta Pace AF, was brought to market without a risk management program. And I don't know all the background behind that. I believe that the predominant reason was sotalol was already on the market for many years prior to dofetilide coming to market. And so the addition of this new indication for sotalol wasn't really a new drug to the market. It was just use of an existing

drug with a different label for a different indication. And so I think that there –- in fact I didn't mention it in our talk, but when we looked, even with our institution, our institution did not add the formulation Beta Pace AF even to the formulary. So all the sotalol patients were actually getting just regular sotalol. And in actuality there was no difference between those drugs other than I think the color of the pill. So in fact there are lot of other issues underlying this as well.

DR. RACOOSIN: You know, I think there's no question that there are older drugs that present risks that are, you know, in the realm of some of the issues that we nowadays deal with, risk management plans. I think, you know, it's an issue with –- as I think you mentioned as the science develops and as safety has become more prominent that, you know, issues get dealt with in the realm of that period. And so now as we think about these issues, and we think how best to make important

drugs available to patients that have, you know, substantial risk, we have a different approach. I suspect if we had the opportunity to revisit some of the older drugs –- and I think that's actually as issues –- new versions of older drugs come up and as new issues come up, they do get revisited in a way. They may not get addressed in the exact same way as the absolute new, but this issue is not –- we understand that this is an issue for older drugs as well. And I think the attention that's being brought to a drug like warfarin now and trying to understand it's polymorphic metabolism and how can we make some progress in the more safe use of that drug by incorporating those aspects of it, you know, is a way to move forward on some of these older drugs.

DR. NOURJAH: We only have five minutes, so you can go ahead.

MS. KWEDER: Sandy Kweder, FDA. I have a related question to the –- there really aren't any good

answers. It's not fair. You know, life's not fair for some of the older drugs.

But one thing that comes to my mind is at what point can some of these programs be lightened? You know, and I wonder, Judy, how much of this –- how much discussion there has been, was for the Advisory Committee in 2003 of do we need this clozaril plan at all. Is this potential toxicity well enough known in the practicing –- this very limited practice community now that this is something that should be in the hands of practitioners? I don't know the answer to that. But it's something that we face for all of these is once there is a RiskMAP, does it need to be in place forever? And how does one decide that?

DR. RACOOSIN: You know, I think that people have a certain comfort level around the current system, at least for monitoring white blood cell counts of clozapine. And so I think there is a certain hesitance to change it

from how it's, you know –- it's been sort of lessened based on the data analyses that we've been able to do. But I think there's generally some hesitance that this has been working, so, you know, we shouldn't change it. You know, I think you would hear on the patient's side that perhaps for patients who have had, you know, done well and not had a problem with agran over a period of time, that they would argue that, you know, at some point we should get rid of monitoring all together. I think, you know, the concern is, you know, people are worried about, well, what about the one case when, you know, someone does run into a problem. But, you know, I think there's some people who are working on the pharmaco-genomic profile of patients who develop agran with clozapine. And, you know, perhaps that is another –- I mean those approaches to identifying patients who are at risk of developing a specific side effect that, you know, as one becomes smarter are using those tools that, you know, it may

change the face of this.

DR. TRONTELL: I actually am not sure in Sandy's question if the –- it would be to take away the mandatory reporting urge is to assume that clinical practice clinicians might continue this, you know, proactive monitoring of patients and whether we'd be comfortable that that would persist, or the infrastructure would persist without the program.

But I know we have just another minute. I actually –- I thought I might press Brian on an issue he's mentioned twice now. And the issue of the purpose of RiskMAPs in fact to discourage use. And in particular, you've referenced the alosetron program. And I think there is no doubt there's been reported here to day that we've had very few adverse outcomes of any consequence with that program. And we have a very low level of use. So I don't diminish that. But I think the question is it may be reduced, but has it been reduced fairly that we may

have sufficiently lowered utilization to a point that there still may remain individuals who might benefit? And might we think to try and get maybe some better measure of low but appropriate use so that we don't just squash it down to eliminate adverse events by just limiting exposure.

DR. STROM: Thank you. But you're raising a number of important points in what you're saying. Firstly my sense is that a RiskMAP which seeks to lower use like that is the last straw. It's what you don't –- you don't want to have to do that if you don't have to. That shouldn't be the norm in designing RiskMAPs. The norm should be to try to steer the drug toward people who are more likely to benefit, or steer the drug away from people likely to harm. And I think that the STEPS program and the clozaril program are examples of things that are more selective in their use.

I think secondly the idea of making sure the

drug is available to people who need it is a very important idea. I think you need to put it in the context of the importance of the drug though, in the context. In the case of alosetron, not to keep picking on it, you're talking about a drug that had marginal efficacy, clearly efficacious, but marginal efficacy on a population basis. The large number of people. It's a symptomatic drug only for a very common condition. That data that were available when it was on the market freely is that 90 percent of the people used it and never took a second prescription. So presumably many people weren't getting benefit from it.

And there was no way no matter how –- we at least on the Advisory Committee pushed the sponsor and FDA to identify the people who are more likely to benefit or more likely to suffer risk. I think if those questions could be answered in the future as well, that's the way to change –- that's the reason to change it. I think when

you have a drug of marginal benefit, but somebody –- there clearly are people who really needed it, who really were sick, who really were benefiting from it, but they were relatively small numbers of people. Then simply putting in place a barrier –- and again it's a symptomatic drug, not a life-saving drug –- simply putting in place a barrier to make it harder was the only solution. And I think in that case, you just have to hope that people can get it. I actually find very reassuring the data we heard that if you look geographically across the country, there weren't parts of the country where people can't seem to get it. The access seems to be proportional. But clearly I consider that an approach to RiskMAP of last resort, not the approach that should normally be used.

DR. NOURJAH: Since you waited patiently, we take your question.

MR. KAHN: Thank you. Sidney Kahn. One thing I wanted to follow up with Dr. Strom's previous answer was

about FDA not regulating the practice of medicine which we all understand. It occurred to me that we already have many, many drugs out there, products which have significant adverse effect profiles and good benefit profiles. And that particularly applies to conditions like cancer, the cytotoxic agents, HIV, anesthetic agents, for example, which in and of themselves if not properly used can be highly hazardous to the patient. And yet they don't have RiskMAPs because they are properly used by specialists in the area. Is this not a potential alternative approach to perhaps obviate some of the onerous provisions of some of the RiskMAPs, and would it not maybe even address the point that Dr. Strom just made about not restricting access inappropriately?

DR. STROM: Couple of reactions. Firstly, in the Lotronex example I actually raised at the Advisory Committee whether the RiskMAP should be simply restricted to gastroenterologists as a solution. I'm a primary care

physician. The people on the committee who objected to that were not the primary care physicians, they were the gastroenterologists. They didn't want it to be restricted. And it's nice to see the data that functionally there has been a big shift that from before the RiskMAP where much of the drug, most of the use, I guess, was from in primary care docs and now it's gastroenterologists. So, yes, I think that is a very viable solution.

The trouble with that solution, the answer I got when I raised that comment, and I think the answer I got -- the objection to my suggestion was very legitimate is one equity, of access. That there are parts of the country that don't have access to specialists. And so given that's the case, that's the problem with that as a solution. You don't necessarily want people to have to come to a tertiary care center to get some drugs. When you're dealing with an infusion drug like Tysabri, it's a

different story. They have to get an infusion anyway. They have to come to a center when you're dealing with a drug like –- Lotronex, that's not the case.

I think it's also different when you look at old versus new drugs besides issues of equity as we were talking about. Is that a lot of how a drug is used is determined by the launch, and how the medical community begins to use it. And in the case of the drugs you're talking about, they're being used correctly presumably or hopefully. They're being used correctly already. We live in a climate now which is very different with the direct to consumer advertising and the desire for blockbuster drugs. And a number of the drugs that have been lost as I mentioned yesterday –- a number of the drugs that have been lost in the last few years has been because of over-marketing. And in many ways, RiskMAPs are in response to over-marketing that in the face of that kind of marketing, we can't trust the medical community to launch the drug

correctly. Once the drug is launched correctly, maybe it should be changed. And this gets back to Sandy's comment about when do you change the RiskMAP and loosen up because now the medical community is doing it correctly.

DR. NOURJAH: Well, this is the end of our session. Please applaud the presenters, and also for yourself.

DR. TRONTELL: We'll resume the final panel discussion before our group –- we'll adhere to our start time of 2:45 as closely as possible. And I'll ask those presenters to come up so we can load their slides.

(Break.)

MS. TRONTELL: A little order of business while we have everyone taking their seats. Again in my many roles in this conference as lost and found, we have a blue tooth earpiece. If you want it, we'll have it at the information desk. Thank you.

I'm Anne Trontell, if you didn't know that

already. And we are in Session 6 which I hope will be a bit fun and a bit mind expanding because we're talking about possible future directions in RiskMAPs, looking to other places where we might learn about how these programs have been applied, or how some of the new technologies that have been mentioned a couple of times already might assist us in making these processes easier, to help people to do the right thing or avoid doing the wrong thing.

So let me briefly introduce the three panelists who will be speaking today. We'll have them speak in sequence and take questions at the end. Our first speaker is Dr. Don Murray, also known as Mac, Lumpkin. He is the deputy commissioner of the FDA for International and Special Programs and clearly a leader in that agency as well as internationally on numerous international –- as well as pediatric issues. He is the key liaison from FDA to the European Union, Japan and other countries, particularly in the harmonization of drug regulatory

requirements. He's held numerous leadership posts in FDA over the years and in the Center for Drugs. He even included in that his oversight of what is now the Office of Surveillance and Epidemiology.

Our second speaker will be Dr. Steven Simon. He's an associate professor in the Department of Ambulatory Care and Prevention at Harvard Medical School. He's also with the Harvard Pilgrim Health Plan. He's a respected health services researcher and a medical educator. He's worked extensively with a number of intervention studies using educational outreach and health information technologies to improve patient safety and quality. He's also a member of the Massachusetts E-Health Initiative, a multi-stakeholder initiative that is expanding electronic health records within the state.

Our final speaker for this session will be Dr. Dan Malone, who's a professor at the University of Arizona College of Pharmacy, and also at the Mellon Enid Zuckerman

College of Public Health. He's an investigator with the Centers for Education and Research in Therapeutics. He deals with pharmaco-economic research and directs the Division of Pharmaceutical Policy within the Center for Health Outcomes and Pharmaco-Economic Research at the University of Arizona. He has extensive experience in pharmacy demonstration projects and economic issues. And so we have a nice blending of both the physician and pharmacists approach to these issues. So with no further ado, let me introduce Dr. Lumpkin.

DR. LUMPKIN: Good afternoon, and let me take this opportunity to thank all of you for staying this late in the afternoon and being part of this session, which as Ann says I hope will be perhaps a little bit different from what you've done over the last day and a half. And that it will give you some ideas about some of the things that might be going on in other parts of the world or other ways of looking at these fundamental questions that

we all have.

Now I have to admit when Ann called me and asked me to do this particular presentation, I was taken a bit back. I said Ann, no, no, no. Why don't you just let me call somebody from the EMEA to come over here and do this, or let's do it by video or something. And she said no, no, it'd be nice to have you come out here and do it. And I said your budget's getting bad, isn't it, Ann? Because it's easier just to get somebody up the street than somebody from across the ocean.

I think part of my disconcert about doing this talk was I've often had to sit in the audience and hear non-FDAers talk about what the FDA does. And while that's often very entertaining and interesting and quite enlightening at times, I have the same feeling if one of my EMEA colleagues was in the room today. He or she might have the same to say about what I'm saying. Because I think often you don't quite get all the nuances, and you

don’t quite get the program exactly as those who live and breathe it every day do. But I’m going to do my best.

And I think many of you in this room I know have actually probably been involved in producing some of the documents and have interacted with the EMEA on their risk management systems approach. And by all means, when we get to the discussion, if there’s stuff that needs to be corrected, if there are nuances that need to be discussed, by all means bring them to the forefront. We’re all in this together as outsiders looking in on a system that are colleagues in Europe are now implementing.

I think one of the things, as we go forward and look at what the European Union has done on this, is that you’ll find that there are obviously a lot of similarities. The questions are the same, the concerns are the same. In many respects, the approaches are the same, but I think what you might find at the end of it is that there are some formalities. There are some mandated

thought processes. There are ways of looking at how one thinks about risk and managing that risk that might resonate and might help enlighten us as we look at how we want to do it in this country.

I think the Europeans would be the first to say that they look at risk management in the wholistic way that we do here. They think of it as a continuing circle. You hear them talk about it as starting with risk detection, going to risk assessment, going to risk minimization, risk communication, and then looking back and reassessing and seeing if you can still detect the risk and going round and round and round in that same circle in trying to reach a certain goal.

With that in mind, the first thing I would like to point out to you is that if you really are interested in seeing the details of how the EMEA is doing this, I would refer you to this particular document on their website. This is their guideline. It’s about 32 pages

long. It's their guideline on Risk Management Systems for Medicinal Products for Human Use. Came out, it was finalized in November of 2005. It can be found and downloaded on their website. You can just go to emea.europa.eu, and in the search engine, type in risk management plans, and this is about the fifth document that comes up. But it's the guideline that really goes into what I'm going to be giving you kind of the 37,000 foot, or I guess to be more correct, the 11,000 meter view on this. I tried to get the spelling right in these, right in the European English sense. I've got to get the measurements right to be a true European talking about this today.

As in most things between Europe and the United States, often the definitions is where the detail hits the road as it were. And one thing I think to start with at 11,000 meters is their concept and the way they define a risk management system. And this is going to be important

because when you get into the legislation in Europe as to what a sponsor of a drug application has to have, each and every one has to have a risk management system for the most part. We'll talk about that and what a risk management system is therefore quite important. And you will see in their documents a risk management system defined as a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products. And very importantly, including the assessment of the effectiveness of those interventions.

Now as I mentioned, in the present EU legislation, there is a requirement that "when appropriate," and we'll talk about that in just a minute, requires when appropriate a description of the risk management system that the company intends to employ when and if their particular product is authorized for marketing in the European Union. What the EMEA has said

is that this requirement in European law can be met by the submission of what they describe as an EU risk management plan as per 4.3 and 4.1.3 of the guidance that I referred to at the beginning. So the risk management plan is the way you meet your legal requirement to have a risk management systems in place.

Now an EU risk management plan has two parts. The first part has two different components, and we'll talk in-depth about each of these components in a few minutes. The first component is described as and called a safety specification. And as I say, we'll talk about what's in this and what the purpose of it is in just a few minutes. The second component of Part 1 is a formal pharmaco-vigilance plan. And then Part 2 also has two components. The first component is an evaluation of the need for a risk minimization activities for specific risk minimization activities, and if there is a need for additional or what they call non-routine risk minimization

activities. Then a risk minimization plan must also be submitted. So if you can imagine if you're doing your risk management plan, everyone has to have Part 1, which is the safety specification, the pharmacovigilance plan. Everyone has to have at least an evaluation of the need for risk minimization activities, and if there is a need for more than the non-routine, then a specific risk minimization plan would be the last component of your risk management plan. You see again why definitions are very important.

Now as I mentioned at the beginning, the legislation says that you have to have this in place and submitted to the authorities there "when appropriate." Now when you look at what they think is when appropriate, it's kind of hard to imagine when it's not appropriate because most of these as you go through, pretty well cover a lot of the waterfront. You can have risk management plans both in the preauthorization life of a product, but

more frequently and obviously we tend to think of them as something that is submitted at the time of a marketing authorization application and something that's really kind of looking at the post-authorization life of a drug. You have to do this apparently when you have a substance that contains a new active substance. If you're doing a bio-similar product, if you're looking at generic where a safety concern requires additional risk minimization activities, if you're looking at even –- what they call a variation which we tend to call a supplement here in this country, if you're submitting a variation for a new dosage form, a new route of administration, or a significant change in indication, you're required to submit a new EU risk management plan, taking into account the impact of the change at that point in time. And then last but not least, you have to do this on request from the EMEA or on request from a European national authority. So again as you think about it, there are not a lot of times where

this is not really a requirement.

And I think one of the things you'll see at the very end that perhaps one of the differences in the way we have traditionally approached this and the way the Europeans tend to approach it is it's quite obvious in my talking with my colleagues in Europe that the premise is everything has one of these, and you have to argue it away as opposed to the premise being that you don't have these and you argue it in. And I think that's kind of one of the fundamental differences in how the approach goes forward.

Now looking at those specific components, the one that they call the safety specification, the purpose of this part of a risk management plan is to help industry and to help the EMEA identify any need for specific data collection and to facilitate the construction of the pharmacovigilance plan. And this is really the part where the sponsor's required to put down in summary format what

indeed are the known important risks of a medicinal product, and then to think through, based on all the information and data they have at that point in time, what are the important potential risks, and what are the limitations that presently exist with the clinical and pre-clinical database. They're required to answer the question are there important missing information that ultimately need to try to be captured. Are there populations potentially at risk that we need to think about, especially an address? Are there outstanding safety issues that we know at this point in time warrant further investigation? What do we know about the epidemiology of the authorized indication, and this is obviously to help set the stage for trying to determine, well, if we know this is the epidemiology of the authorized indication, how is that going to impact on the kind of risk management studies, the pharmacovigilance that we're going to be doing on this particular product?

Are there any potential class effects that need to be taken into consideration? And is there a potential for overdose? Is there a potential for transmission of infectious agents? Is there a potential for misuse for illegal purposes? Is there potential off label use that raises safety concerns? And specifically, and dear to my heart, is there a potential for off label pediatric use that raises concerns? So this is the framework. These are questions that are there that every time you do a risk management plan, the safety specification has to at a minimum address these issues and say this is what I've thought about, this what I think the data are telling us, and this is where I think we need to go relative to the issues we know about and the potential that I can reasonably think based on the data I have might indeed occur if this product were to be authorized in the European Union. So that's the first part of Part 1.

The second part of Part 1 is based on the safety

specification, based on the arguments that you've made in the safety specification, what are your proposed actions to address these particular safety concerns? And this is in essence your pharmacovigilance plan. And generally the pharmacovigilance plans are divided into two components. One is one that is called routine pharmacovigilance. And this is basically the passive system that we've used in this country and that we've used in Europe for many, many decades. And part of the issue here is making the argument that that is adequate. If you think the passive systems that we have used in the past is all one needs, then you have to make that argument. If not, then you have to say based on –- and it's in Annex A of this document –- what non-routine pharmacovigilance activities would be appropriate to answer those safety concerns that were raised in the safety specifications? And they go through and they talk about things near and dear to all of your hearts. And you guys know infinitely more about

these than do I, but obviously do you need an active surveillance system as opposed to a passive surveillance system? If so, do you need to think about using sentinel sites, an intensive monitoring scheme, or prescription event monitoring kind of system, registers comparative observational studies, cross sectional studies, cohort studies, case control studies, other novel designs, clinical trials, large simple trials, drug utilization studies. They're all out there. These they all kind of lump under this non-routine pharmacovigilance and if indeed you can't answer the safety questions and concerns that are raised in the safety specification, then by simply having routine passive pharmacovigilance activities, then what of these non-routine pharmacovigilance activities do you think are going to be appropriate. And then how are you going to go about indeed implementing those that you think are appropriate. So that's Part 1. Again all risk management plans have to

have those two components of Part 1.

Then you get to Part 2, and the first part of that is the evaluation for risk minimization activities. And this requires the companies to look at each risk that is identified in the safety specification and say do I need to do more than the routine risk minimization activities. And we'll talk about what routine is. And if not, if indeed one doesn't believe you can handle the risks effectively with only using the routine risk minimization activities, then what do you need to do from the perspective of a more intense risk minimization plan to deal with the concerns that are there?

Now the routine risk minimization activities are generally lumped under these particular things. These are the routine warnings that you find in product information and product labeling and packaging, and in the patient information leaflets. And all of you know with the centrally authorized products in the European Union, each

one is required to have a patient information leaflet that is authorized by the European Union at the time the product is authorized for marketing. So it has both a professional, what they call the summary product, summary –- the SPC, the summary product of characteristics and the patient leaflet.

The other thing that you're required to look at from risk minimization from the routine perspective is there a potential for medication errors. And if there is a potential for medication errors, are these things that can be addressed by product information, by labeling, by packaging, by the patient information leaflet. And I've always thought that they put medication errors in here because obviously a lot of the concern about medication errors could potentially be addressed using the more routine risk minimization activities that they outline here.

Now should you believe that the risks that

you've identified cannot be handled just using the routine risk minimization approach, then you have to put forward a risk minimization plan which would include other kinds of activities. And many of these are the kinds of things we've seen in this country, kinds of things you all have been talking about and have had several examples of. One involves the provision of information, one is the additional educational materials that might have to be produced and distributed, one –- they call it the legal status of medicine. This really has to do in the way we look at things with restricted distribution and restricted use by certain –- people with certain professional qualifications. They obviously have the ability in Europe to control at the pharmacy level in certain ways that we do not here at this point in time. They look at perhaps using control of packaging size or the validity of a prescription, and they mean that in terms of time, or the time that a product is valid for being used by a certain

patient, the use of informed consent and the use of patient registries. So that would be a risk minimization plan putting forward which of those or others do you think are needed in order to make, as we just heard in the last session, the product available with a positive benefit to risk perspective.

And in the last part, which I think again is one of the most important and one of the most interesting parts, is that in the risk minimization plan, you have to put forward how you're going to assess the effectiveness of the plan. What are the metrics that should be predefined and validated. What is going to be the timing of your assessments, and what are the potential responses that you're going to take depending on the results of your assessment. So if you find out at a certain pre-specified point in time that your risk minimization plan has not accomplished the goal of your plan, then what indeed might be the next steps that you would take at that point in

time.

Now I thought it was interesting –- I mean this is their program. This has been in effect now for about a year and a half. And last week in Atlanta at the DIA, one of our colleagues from EMEA actually gave some statistics that they've had since this was put into effect. They've had 75 centrally authorized products since this time in 2005, as we said at the beginning, since most do indeed have to have a risk management plan. Sixty-seven of the 75 had risk management plans. And of those 67, eight had additional risk minimization plans added. So it kind of gives you the idea of most everybody gets Part 1, both sections, and the first part of Part 2. Only about 10 percent were into having a much more formal restrictive risk minimization plan.

So I think in summary as you look through here, some of the things that are interesting I think is we look in from the outside is that you see in the European system

there is indeed a legislative mandate for risk management plans as defined by their guidance. And as I mentioned at the beginning, there is I think this underlying premise that you will clearly have one of these. And not having one is the exception. You have to argue your way back as to why you don't need to have this kind of thing.

So again I hope this is helpful. I hope it gives you an idea of how are colleagues across the sea are indeed looking at this. And I look forward to discussing it with you. And as I said at the beginning, if any of you have done these, if you've been involved with the EMEA, there are nuances here that I've not picked up on. We're all in the same boat, so I look forward to talking with you about it. Thanks very much.

DR. SIMON: Thank you. I'm Steven Simon. Thanks for the chance to be here with you today.

As Max said, Ann spoke with us in preparing for this presentation and told us to try to make it fun and

try to stretch our minds a bit. So hopefully we'll get there today. And hopefully I've left ample time for discussion as we get to the question and answer period.

So my disclosure is I don't have any industry funding, either PhRMA or HIT industry. My funding is from AHRQ, American Diabetes Association, and the state of Oregon.

So what I thought we would talk about is health information technology for medication safety in a generic way. And not limit this exclusively to RiskMAPs, and I think that picks up on what we heard from the previous session, which is that there's some continuum, some spectrum where RiskMAPs end and where clinicians and systems take over and implement interventions for patient safety and preventing medication errors. So what I'll talk about today is hopefully applicable in some way to evolution of RiskMAPs. But if not, it's certainly going to be applicable for considering implementation,

interventions and medication safety more broadly.

What I thought we would talk about in terms of HIT for medication safety really is, you know, it's a broad area and you could talk for hours. One could talk for hours, but I won't. We'll talk about an example of clinician targeted interventions, and I'll focus on computerized clinical decision support. And then you could talk about a whole wide range of patient targeted interventions using health information technology, web-based outreach, e-mail interventions. But I won't talk about those. I'll limit my comments to examples of using automated telephony or automated telephone outreach in particular with speech recognition.

This is an example of work done with clinician targeted intervention supported by AHRQ funding to the HMO Research Network Center for Education and Research on Therapeutics patient safety grant a few years ago. We did several intervention studies localized at Kaiser

Permanente the Northwest in Portland, Oregon. And these interventions using clinical decisions support, alerts and reminders in the computerized order entry system, we're targeting three areas. We're targeting reduction or prevention of medications that are generally intended to be avoided in the elderly so-called Beers criteria medications. Other intervention alerts were intended to prevent drug interactions, and then we also had a set of interventions I won't talk about that were intended to reduce errors of medications where dose adjustment for patients who have renal insufficiency should occur but wasn't occurring. I'm only going to talk about the first two examples.

The first one is work led by Dave Smith at Kaiser Permanente of the Northwest and looks at reducing medications that are potentially inappropriate in the elderly. So here's an example, an example of the kind of alert that clinicians saw as part of this study. And what

you can see, if I can get the pointer to work, what you can see is the clinician using the computerized order entry system would have typed in a medication, might have typed in diazepam, the generic form of Valium, and would get this alert. In the middle it says, “This is a formulated drug but use caution in the elderly. This medication has a long half life and may cause adverse events, such as the risk of falls and fractures in the elderly.” Recall this study was done several years ago, and, you know, there’s more recent data published in the annals of Internal Medicine this year that suggest that long acting benzodiazepines may not be so harmful in the elderly. But be that as it may, at the time the conventional wisdom and prevailing knowledge was that these medications ought to be avoided in the elderly. So this alert would occur and any time you prescribe this medication for any patient, and you’re ideally supposed to change your prescribing. So you’d work your way down from

the diazepam, the order initially, to one of these three alternative medications suggestions in the middle, oxazepam, or peroxetine to treat a patient that might be having anxiety.

So the question you have is, well, does this intervention change behavior? And again as Dr. Strom was mentioning, the subjects of this kind of research are the clinicians, the prescribers. So can you change the way the clinicians prescribe? Do you reduce the medications that you try to reduce, and conversely might you see an increase in the alternative medications, the “preferred medications.” So what you can see from this figure, first focusing on the top set of graphs, these are use of the non-preferred agents in these interventions, the so-called –- some of the so-called Beers criteria drugs, long-acting benzodiazepines. And the dark figure on the top shows that prior to the intervention, prior to the implementation of these clinician targeted clinical

decision support alerts, there was a rising trend in the use of long acting benzodiazepines and other Beers criteria drugs that are thought to be avoided –- should be avoided in the elderly.

And after the intervention, you saw a step-down, a decrease, and then a decreasing trend in the use of these medications over time. That occurred in people who are over age 65. That's the dark bar, the dark set of data points in the top graph. The gray data points in the top graph are people who are under 65 for whom these alerts and the change of practice really isn't as indicated.

So it looks like it worked. And the bottom set of graphs is the converse. So if you apply these alerts, do you see an increase in the use of the alternative or preferred agents? And the answer is yes. It's not quite as dramatic, but looking at the bottom set of figures, you can see there was already a slight increasing trend in the

use of these alternative preferred agents, and that actually had a slight step up in a continuation. Not as dramatic, but clearly these alerts work to reduce prescribing of these medications that were trying to be reduced.

Similar intervention, this work led by Adrienne Felstein also at Kaiser Northwest, is can you prevent warfarin drug, drug interactions, and this is similar to what Dr. Strom was mentioning. This work put in place alerts in the order entry system. Whenever warfarin was co-prescribed with acetaminophen containing narcotics, metronidazole, fluconazole, non-steroidals, and then co-trimoxazole or trimeth from sulfa triazole. These alerts occur whenever co-prescribing was happening in real time, or when both medications occurred and appeared to be active in the patient's medication list.

Here's the kind of alert that a clinician would see when prescribing. The clinician would enter the

medication order, the computer would detect the presence of co-prescribing that was targeted for prevention, the clinician's alert would say this is a safety problem. And that's notable because clinicians in many systems, like Kaiser Northwest and the place where I work at Harvard Vanguard in Boston, are bombarded –- is probably a fair word –- with alerts all the time. Some for safety, some for formulary restrictions, some because it's a cost –- preventive cost reduction measure for the patient. This tells you it's a safety alert, and that was intentional. And there's a potential drug, drug interaction. There's a risk of bleeding when you prescribe acetaminophen containing medications concurrently with warfarin. You should think about doing something different. You'd press okay, be given an opportunity to select an alternative medication instead of acetaminophen with codeine. You might be prompted to select a different agent.

And here's the result here. You can see a

similar kind of graph as before. There was prior to the intervention on the left side of the figure, a pretty stable monthly rate, monthly number of co-existing prescriptions of drug, drug interacting prescriptions. And then after the intervention was implemented, there's a step-off, as well as a downward trend in these co-existing, co-prescribing events.

So it looks like this kind of intervention works for changing behavior. And this is not a hospital-based system. This is Kaiser Permanente of the Northwest. So the question was raised earlier what about outside of academic health centers? This is some evidence and there's other to show that these kinds of alerts can work.

So can computerized clinical decisions support be used to prevent clinicians from prescribing, that is in a RiskMAP kind of setting, or at least to ensure they prescribe with precautions? These data would suggest that it's possible, and we'll set systems be acceptable to the

clinicians. That's a bigger question. You know, there's been plenty of failures of implementation of HIT in some places and computerized order entry in places where clinicians are overloaded and bombarded with alerts and other problems and clinicians reject it. And as others have said today already, clinicians are faced with lots of –- and lots of lots of alerts and reminders. And there's always the problem if it's too much, will they just be blown off and ignored.

Let me shift gears and talk briefly about a patient directed intervention, automated telephone outreach. And by this, this sort of telephony intervention, we think about the possibility of using interactive voice recognition or speech recognition with automated telephone calls, a computerized system placing telephone calls to thousands of patients simultaneously, or over whatever time period you like, with an attempt to engage patients in a variety of different clinical

relevant behavior. And I'll show you some examples.

This kind of automated telephone outreach approach has been used, can be used without speech recognition. So, for example, you could have a computerized system call patients, provide them a message and not have an opportunity for any kind of interaction. It's been used in the past with automated calls out to patients with opportunity for touch tone responsiveness. And then the more recent modern implementation is with interactive voice recognition or speech recognition, interaction between the responding patient and the system. This can be done in an automated way so you're not relying on a human person sitting by a phone dialing and dialing over and over gain. The multiple call attempts can be done multiple times of the day to try to reach people to maximize the reach. And there's also an opportunity to leave a message. These automated systems can leave a message either on someone's home answering machine voice

mail or actually with a live answering person, leave a message with a call back number. And then the attending participant can call back in to engage in their intervention.

So here's the examples of where it's been used, and then we'll hopefully ask you to think about where this would fit in with RiskMAPs and other medication safety interventions.

So automated telephone outreach with or without speech recognition has been used to enhance influenza immunization rates, to improve cancer screening, to improve osteoporosis screening. It can be used to do case finding and prevention of chronic conditions so you can call large numbers, large populations of individuals, health plan members, for example, to try to determine if people have evidence of hypertension that may not have been detected clinically or not yet treated. Even lipids and diabetes. People who may be actually quite healthy

who haven’t had testing, screening, testing done, it might be appropriate. And then among a sicker population, these kinds of interventions can be used to improve diabetes self-management, can be used to enhance individual’s care of congestive health failure and asthma, for example.

So what are the potential uses of this kind of automated telephone outreach for RiskMAPs? Well, example would be you could use a telephone system that could be triggered by the dispensing of medication to call a patient soon after he or she received it to confirm the patient actually got it, make sure the patient understands what she has, make sure she got the right medication, and make sure she knows what the risks are related to it. And sure, you could do this with a message outgoing, leave it on the answering machine, or just dump it into the person’s mind, but with this technology, there’s the opportunity to build in interactiveness. And this technology in going forward is likely to be able to pick

up on a hesitancy among a patient who says, you know, I got this medication. I'm concerned that, you know, I'm bleeding out my ear, is it normal. So there's real opportunity to detect adverse drug events. And then more for improving quality and less for RiskMAPs, there's the idea of ensuring adherence and appropriate follow-up.

We don't know if this kind of technology is effective in a lot of settings. And certainly we don't know if it's going to work. And I hope in the discussion session, we'll have some time to hear what people's experience is with this kind of technology in medication safety and ideally what could be learned from RiskMAPs.

I guess just the last comment is it's absolutely clear to me and I think to most that HIT interventions, all interventions to improve medication safety and RisMAPs must be evaluated. And we evaluate them any way we can, whether it's in a randomized trial or using quasi-experimental methods, using interrupted time series

designs. And I think that the other point is that HIT is not a panacea. And I think the role that we have, the role the regulatory agencies have, that academia has, that health plans have, is to test these kinds of interventions, figure out what's effective, what's cost effective, and then implement them more widely once you know they work. Thanks very much.

DR. MALONE: Well, thanks for sticking to almost the end. Dr. Tilson, I'm sure, will be paying attention to this so he can make some notes for his last presentation.

But I'm going to try and bring a different perspective. Ann, did you look at my slides before I -- okay, we're going to get a little fun at the end. So I thought you might have taken a look at my slides ahead of time. So have a little surprise.

Anyway, I'm going to talk about risk in pharmaceuticals from a different perspective. And one of

the ways I want to frame this discussion, kind of relates back to full circle to my dissertation which examines strict liability actually with pharmaceuticals and Comment K, which is a component of strict liability. It's part of the restatement of torts, the second –- we're –- pharmaceuticals are specifically excluded from strict liability under the notion that they're unavoidably, unsafe products. And that this comment goes on to state that there's a number of reasons why we want these products around, and why we don't want to apply strict liability to them. And that generally speaking, that the benefits to society outweigh the inherent risk of these agents. And I think to some extent when we start talking about specific agents, we tend to lose sight of this notion that all these products that we've been talking about, and even ones that we haven't been talking about, have risks. And that there's this continuum of risk that conveys from over the counter products through to the very

restricted distribution systems.

Now one of the problems with risk is that it brings on liability. In many of the things that I'm going to talk about with drug interactions is evolved because of a threat of liability. And what happens is those systems have driven our health information technology programs to not work by and large in my opinion, especially with drug, drug interactions. And I'll talk more about that as I go through.

Now we commonly use this as part of our Arizona CERT montro with regards to re-evaluating various slices of the Swiss cheese with regards to where can we close the holes to prevent the ADR from getting to the patient? And we've been doing studies to look at various components, including precriber knowledge, computer systems, pharmacist's knowledge. And we're kind of foraying into patient risk factors. We've talked about other things here about drug administration, patient monitoring and

patient education that could reduce these adverse events. So I'm going to talk to you about some of the things that don't work with drug interactions, focusing more specifically on the pharmaceutical side, but some of these same slices can be applied directly to the risk management programs.

Now the first area I wanted to briefly touch on was computerized (indiscernible) of potential drug, drug interactions. And many of you know, but maybe not all, that every time you fill a prescription, the computer systems are now doing a check to make sure that there's not interaction in place. In fact, that is ubiquitous. All the pharmacies have implemented this sort of check. It has become the legal standard. So these systems perform a routine check of what medications are in your profile, and they match it up against the new drug going into the system, okay? And it provides an alert back to the staff.

Now the type of alert it provides back, and it varies depending on the vendor, it depends upon the chain, it depends upon how the pharmacy staff may or may not customize that information. Now one of the problems that we get into with these sorts of interactions, or these sorts of alerts, is there's multiple ways to classify interaction. And let me just highlight some of the issues there.

We did some work sponsored by the CDC several years ago that looked at various compendium with regards to their classification system for drug interactions. And what you see here is across these well known and accepted drug compendia, our different methods to classify drug interactions. And you can see that there's nothing consistent across these four compendia that many of us in the pharmacy world would stock on the shelves in terms of something we go look at, a potential interaction. And in fact, if you tried to cross reference these, there's very

little information that is consistent across them.

We did a study where we took the major interactions listed in each of the compendia and cross referenced them across them. We essentially tried to see what degree of concordance there was across these compendia. So in essence we evaluated 406 different interactions, and only nine of those 406 were listed as a major or the top level of severity across all four compendia. There was no agreement whatsoever among the compendia. And in fact if you even dropped the criteria to three of the four, when we have an additional 35 interactions listed, there was no consistency between these compendia on how they classified risk.

That’s really important when it gets to a risk management process is that we have people who are making decisions about what’s risky and what’s not in some of the isolated vacuum in terms of these are editors evaluating very scant data trying to make a decision of is this a

moderate or is this a major interaction. If we're going to apply these same sort of technologies to risk management programs, we need to be more precise, and we need to be more consistent across our systems with regards to what level of risk we're talking about because people like to think about things in very discreet, you know, operational constructs, and in saying that, well, this program has all of these elements, you know. It's going to drive practitioners and pharmacists away from using those products if as compared to saying this is a high level risk product. These are the elements that are going to be part of that risk management plan.

Another issue is that even when you operationalize interactions into your systems, the systems don't work. This is a classic study by Tom Hazelet at the University of Washington, who looked at in-store pharmacy software systems ability to detect drug, drug interactions. I want to have you focus on the sensitivity

column here in the sensitivities, the ability to detect interaction when we know an interaction is present, okay? And the average across nine systems that he evaluated, which represented over 500 pharmacies in the state of Washington, was barely over 70 percent. The best was 88 percent. And then there was one particular organization which only identified 44 percent of the interactions that they had put through the system. These are pretty bad.

We thought, well, you know, maybe it was just a point in time. So we repeated the study a couple of years ago, and the good news is we've gotten a little better. But we're still not 100 percent. We evaluated pharmacy chains that represent about 2,000 pharmacies nationwide and still we have a gap between what is optimal and what is happening.

We also went into seven hospital systems. They performed rather poorly. And in fact I would hate to be practicing pharmacy if the system were only 15 percent of

these interactions were cut. But that is present into today's marketplace.

So why do these systems fail us? What's going on? Well, there's a myriad of factors. You know, like I mentioned earlier, poor definitions of what significant means, okay? The risk benefit of formula is determined in subjective manner, you know. Unlike many of the products that we're going to be dealing with the RiskMAP, we have very few studies to support interaction data. Most of them are theoretical, a few of them are animal, but only a very few situations do we actually have good re-inimized data. We have a few people evaluating these criteria and operationalizing it.

Another issue –- and this is kind of endemic of the system is there's also the ability to enter prescription data without necessarily linking it to the underlying database that supplies the drug interaction system. And this is something that happens, happened to

be when I practiced pharmacy. You get the prescription order for the new product, and you haven't updated your software, and yet you need to fill that prescription. And what happens is that order is perpetuated, not just for that patient but for all other patients that use that drug lookup field for. So not only could this problem lead to just a single problem with the interaction. It could lead to multiple patients, you know. So we have an issue of real time with regards to having this information in the database at the time the drug is released. And there is certainly an opportunity for error if you don't have it. And then there's an issue with regards to how you operationalize your NDC codes, and I'll talk more about that in just a minute.

Another thing that we want to talk –- I want to briefly bring to your attention is the issue of pharmacy benefit managers, which, you know, allow us to do real time checking for drug, drug interactions. And this is a

very valuable asset to our drug safety systems because if the patient received medications at two different pharmacies, here's an opportunity to actually catch that. And while I'm on that point, if we pulled drugs that have a RiskMAP program out of the normal distribution channel, our ability to check for drug, drug interactions diminishes or goes away completely. So that's something to keep in mind as we develop these systems.

But back to PBM's. So these PBM's –- and I heard somebody mention it, what's a hard edit, what's a soft edit. Generally speaking most of the pharmacy benefit managers, what they do is they go through a number of eligibility checks to make sure the drug's covered, patient's covered, the insurance is covered, all these other checks, and these are considered edits. By and large, the industry uses almost exclusively soft edits. And in fact when we've asked PBM's to work with us on studies and implement hard edits, it's very difficult for

them to get it done because their clients, the employers, the insurance companies, don't want patients complaining that they can't get the medications that they want when they want them.

Anyway, the PBM's are very effective at processing claims. They can process the claims rather quickly, provide the message back to the pharmacy. So not only do you have your in-store system giving you an alert, but when you submit the claim to the PBM, you're getting an alert back there too. So guess what we've had happen? We've got this huge problem in our society right now, at least our medical system, where we have alert fatigue. Pharmacists just ignore these alerts. We've seen it through studies that we've done. John Murphy from our group has done it. Michelle Chui, Mike Rupp did one of the first studies. Most of these alerts are ignored, and rightfully so. They should be ignored because they don't really represent harm to the patient. But the problem is

that not every one of these should be ignored. And yet we're seeing that these systems continually lead us to ignoring this sort of information. Lots of reasons for this.

One of the issues that was mentioned yesterday by many of the pharmacy advocates was the issue of workload and how the workload –- disturbing the workload flow can affect the ability to dispense medications. We've recently published a study looking at how potential drug, drug interactions occur as a function of a pharmacist's workload. And we found that as pharmacists get busier and busier, they dispense more potential drug, drug interactions, okay. And that's accounting for all sorts of technologies that they can employ to counteract some of the workload issues. But that's something that we need to kind of keep in mind is that to the extent that these programs interfere with that workload issue, we're going to see decreased ability to actually prevent harm.

Another particular study I thought I'd bring to your attention, Marcia Rable at the Kaiser Permanente, Colorado recently did this analysis, and it's in process. I think E-print is available. This is a (indiscernible) trial to compare computerized alert system to pharmacists for Category D or X medications for women who may be pregnant, okay? Well, the main finding is the intervention had an effect. Rates of these medications, the D or X category medications, went down in the intervention group. The bad news is the study was stopped. The study was stopped for two reasons. The first reason is that the system had too many false positive with regards to identifying D or X medications. Meaning that albuterol, inhaled albuterol was defined as a D medication. So, you know, guess what the pharmacists wanted to do with that information? You know, they want to basically throw it out. So two out of every five alerts was for albuterol or a similar type medication.

The second issue was here in a very closed system, we couldn't translate the information about the pregnancy status of the woman to the pharmacist in a timely manner. And that pharmacists were saying, well, this woman's pregnant. I shouldn't dispense that when in fact they actually delivered the baby, they had an abortion, or they had a miscarriage. Now this is an enclosed system, and they couldn't do it in a real time. So when we start talking about trying to implement these health-aid IT programs to do risk management programs, I have a real concern about our ability to present the information to the person who needs it in the time that they need it.

I briefly want to –- I know Dr. Simon really addressed the computerized physician order entry. I just want to hit this study real quick. This is a study that we have coming out in the American Journal of Managed Care where we looked at VA prescribers reasons for overriding

drug, drug interaction alerts. So what we did is we did a retrospective study of six VA medical centers to examine what prescribers did when they saw a drug, drug interaction alert, okay. And the VA uses two levels to classify drug, drug interactions, either critical or significant. For critical interactions, theoretically speaking, the VA computerized physician order entry system requires the physician to enter something, okay? And the goal of which is that when the order verification occurs, the pharmacist can then determine if that's a valid reason to allow the prescription to be dispensed, okay?

Now these alerts are set at the national level, although individual VA's can modify them. In addition, some VA's actually instituted a response to significant interactions. So what happens when these alerts are implemented? Well, for critical interactions, which constituted 72 percent of our sample –- we evaluated over 15,000 override reasons –- 47 percent of the time did we

have a reason to evaluate. They hit the space bar to get through. And of those 47 percent where we did have something to evaluate, only 20 percent of the time was considered useful for the order verification process. So most of the time it was junk. You couldn't use the information. And for significant interactions, actually worse data.

So what this tells me is that requiring physicians or prescribers to enter something in order to proceed to the next step, this is a false stop. You have to stop and put something in a box, you know, as a hard edit. Requiring that doesn't necessarily get you what you need to know, okay.

So issues relevant to RiskMAPs, poor specification of risk, we've got to do a better job specifying risk. And along with that, one size does not fit all. And we have multiple (indiscernible), multiple systems, which has created a really problematic situation

right now I think in that how do you reconcile some of these. And I heard some excellent ideas in terms of creating national vendors to actually handle RiskMAPs across all products. We certainly need that sort of situation in the interaction side.

Setting risk levels. I think –- and this is an opinion –- that if we have MCO's creating their own RiskMAP situations in terms of what they're required the pharmacists to do, then all of a sudden, you have in a fee for service market where you have pharmacists interacting with multiple organizations, you have a situation of confusion. And, you know, what am I supposed to do for this provider. And, you know, physicians don't like that either.

There are some new models being developed. And I don't want to appear to be an advertisement for any particular model, but I do know of some other models that are occurring out there. One is this Mirexa Corporation,

which is kind of trying to organize pharmacies to provide some sort of web-based platform for doing these things. So they're trying to create a network of pharmacies to provide some of these things, and this is advertisement as I'd like to get, but they're doing a number of things trying to track adverse events and integrate this information into a web-based portal. We probably need more of these systems out there for a risk management program.

Other things that I think are relevant. One is you need to be able to verify your document 24/7, 365. In my life as a pharmacist before I became a professor, or full-time professor, I worked the midnight shift occasionally. And you'd be surprised what patients show up at your pharmacy at 3 in the morning and what they want. You've got to have those decision support systems available because you're really busy at 3 in the morning, believe it or not.

Some other issues. Don't assume that linking NDC will be successful. We've seen situations where that doesn't work. As I mentioned earlier, new drugs are often entered manually. Yes, re-labelers occasionally like to repackage resulting in new NDC's, how those get transferred to the pharmacy can be problematic. Pharmacists are extremely busy. Very busy in these days, and with the current work shortage, it's really difficult to change your practices.

And Dr. Trontell asked us to talk about perhaps institutional-based systems. You know, we have a lot of silo computer systems out there, even in hospitals. And that is problematic because even in some of the best environments for managing risk, we don't talk to each other very well.

Now here's my diversion real quickly. So we've done a lot of automation, and I think that we need to implement automation very carefully because there are

adverse consequences to doing things just because it sounds good. And the analogy here is going to be stretched a little bit. But this is, you know, this is the end, so to speak. We all know how to use this particular device. I mean it's self evident. There's really not a user's manual that needs to go with these things, and they work reliably, okay. Well, recently I was traveling back from Washington, D.C. to Tucson, Arizona, and I had a change of planes in Houston. And the Houston airport has implemented these throughout the airport. And these are wonderful devices when they work properly. But when they go off every 10 seconds while you're on them, and essentially give you a carwash when all you wanted was a biological relief is very frustrating. So we need to be careful on how we use automation. And my thought on automation is that thinking ceases when we implement automation strategies. People like to just stop thinking when they say the computer can

do it all. ASDF becomes a four-letter response to required hard edit. And if you look at your computer keyboard, ASDF is the left-hand keys.

Implementing hard alerts can have adverse consequences. People act like water. They tend to find your cracks, and they find work-arounds. So they're going to seek –- some are going to seek the lowest point, the easiest way to get the job done. So you have to be very careful.

And I heard earlier this comment that I just need to reinforce it. Details are everything to get by in. They have to work consistently all the time without exception. And those details are really tough to implement in medicine. So with that, thank you very much. I appreciate your time.

DR. TRONTELL: We're nearing the end of our day. We ran a little long on our session. I think we'll do like the good TV programs, run right into the next. Let

me invite our panelists to come up to the front of the room and see if we have any questions from the audience on health information technology recognizing the lateness of the hour.

The takeaway message as I took, and I'm sure Hugh will disabuse us of anything else that he might have missed, but clearly we have a lot to learn from our international colleagues in that in some –- it could always be worse. They look at risk minimization as the default. But let me invite Marietta to the microphone.

MS. ANTHONY: I'm Marietta Anthony from the Arizona CERT. Actually I have two questions, but I'll start with Dr. Smith, and that was in terms of your studies, I noticed that there was –- seemed to be a certain level that you got to, and I wondered if you had any thoughts about how you could decrease that level more of encouraging prescribers to switch to other drugs?

DR. SIMON: I guess one reaction is that it's

true that these interventions with HIT didn't completely fix the problem. And we wondered the same question, so we actually superimposed on these order entry interventions academic detailing, group academic detailing, to see if actually talking with the clinicians about the alerts and about the alerts and about the barriers to their prescribing within the intended way to get them to articulate what are the reasons they're doing things in a way that might not be what you want to do didn't actually make any difference. So despite superimposing an educational intervention that has a lot of evidence and proof behind it, we couldn't bring it down further.

One question I have is whether these trend lines continue down, and if we go back and look now two or three years later, have they continued to reduce the unintended events. I don't know the answer, but I think what's going to come next –- is going to have to come next are multi-model interventions that try not just alerts to the

clinicians because we know those have their limits and there's problems of alert fatigue and other, but it's going to have to involve interventions that target the clinicians, their support staff, targeting patients. And where the stakes are really high, there's going to have to be multiple prongs at once to prevent the adverse consequences.

MS. ANTHONY: And then, Mack, I had a question for you about the risk management plans. Is there any comparison with the Phase IV studies? And then also in terms of effectiveness and what's accomplished, and, you know, how many times Europeans actually fulfill the risk management plans compared to the Phase IV studies.

DR. LUMPKIN: I think it's a good question. As far as I know, it's still early in the process. So this has really only been going on for about a year, year and a half in Europe, and so I don't know if there's any data at this point in time that would allow us to do it. But I

think it's an important question and one we, and I know our colleagues there, are going to be looking at.

MR. LAMBRECHT: Raf Lambrecht, Fibrogen. I have a question for the FDA actually. Has FDA received risk management plans for a global new drug application and a copy of the European one?

DR. LUMPKIN: I hear from Cedar that they don't know unless there's somebody else from Cedar who might.

MS. KARWOSKI: Claudia Karwoski. Our team very often receives a duplicate copy of the EU RMP plans, and we review those as well. So, yes, we get them quite frequently.

MR. LAMBRECHT: As a follow-up question, does have actually welcome the plans in that structured way?

MS. KARWOSKI: Well, I think that –- I mean clearly not all of the plans that we get are going to be for RiskMAPs or something that requires something more than routine. So I mean in most cases, they have been

routine sorts of activities, and we've in a lot of cases agreed with those approaches. When we see a need for maybe some things that go above routine, we have asked that they submit additional materials and things that are more consistent with what is in our direct guidance is. So while they have been useful, we in many cases had to ask for more information.

DR. LUMPKIN: It would seem that part of the -- you know, if you look at the thought process and the idea of having this prospective thought process that looks at what potential risks might be there, that that element would be very helpful and somewhat universal. The issue of then how to manage it is going to have local ramifications because the tools that you have to manage are going to be in many cases unique to various jurisdictions. So just looking at the whole thing and saying, yes, this is good enough for Europe, it's good enough for the U.S., I think goes to a certain point. And

then you have to look at the reality and what's happening within your own local jurisdiction when you get to the tools.

DR. TRONTELL: Yes.

MR. OKORIE: Yes, this is in addition to the follow-up question. My name is Ernest Okorie from (indiscernible). Based on the EU and the FDA, has there been any approval of new drugs comparing EMEA and FDA because in EMA, it is required to provide the RiskMAP?

DR. LUMPKIN: Could you clarify a little bit more exactly? Yes, you're right. They're required to do the risk management plan in Europe for the most part. What's the comparison that you're interested in? I'm sorry.

MR. OKORIE: Is there any approval, for example, the approval rate of new drug, is it more in Europe more than here in the U.S. or vice-versa because of the –- they have to provide the RiskMAP in Europe?

DR. LUMPKIN: I don't know that we have any data that says the RiskMAP has kept products from going to Europe. I mean obviously you can look at individual products. There are some that are available in Europe that aren't here and vice versa. But unless others have heard along those lines –- I don't know. Have any of you from industry here that would 'fess up that you submitted here and didn't submit in Europe because of this? I didn't think so. Unfair question on my part.

DR. TRONTELL: Last question.

MR. TUCKER: Ed Tucker from Bayer. I want to ask about alerts. The alerts I've seen in the last two days don't appear very alerting. Maybe Hugh Tilson will add that to his list. Have there been any studies to show effectiveness of those alerts and changing the quality of those alerts?

DR. SIMON: We think the same thing. You know, as both the researcher and the practicing physician, I can

say a lot of the alerts that I see, they're boring, they don't get your attention. They're easily maneuvered through. There's lots of work around –- so I think there's clearly, you know, at least 10 commandments by which one should develop alerts. David Bates wrote about those. Others have written about the things that make alerts effective, and that's borne out by evidence by randomized trials.

We've taken an effort through another project I haven't shown here to build alerts that are colorful, that are engaging, that give clinicians what they need. So clinicians don't just want to go through the administrative hurdle of clicking yes or no or accept the alternative. We think that what they'd like is to have a button that would give them information to talk to the patient about why I'm not giving you this drug, or be able to print out an information sheet, or be able to give them some information that actually makes them feel better

about making that decision and do something with a little more, you know, vim and vigor. So I think the answer is you're right on. We're working on it.

DR. TRONTELL: Steven, can I follow up on that, and also Dan. You know, we heard in some of the other sessions that involving the stakeholders and the design of RiskMAPs was very important and some of your work with these various HIT systems. Has there been any effort to try and build it around clinical practice or preferences?

DR. SIMON: So whenever we've done building new interventions and alerts in order entry or for medications, for laboratory monitoring, we've always gone to the clinicians and tried to get their feedback on what works, what doesn't work, and then implement based on that and make modifications. But I guess I have to say one lesson is even if clinicians tell you they want something one way or one thing doesn't work, when you put it into practice, it doesn't always mean it's going to work the

way they said it's going to work.

DR. MALONE: I certainly have less experience than Steve on this issue. I do know that there is a process where many organizations go through to vet their systems. On the pharmacy side there's a lot of input from the end users into how they develop their systems. That said, there's a lot of room for improvement there. And there is –- we didn't discuss a lot about the vendors who provide this information, you know, such as First Data Bank, Metaspan, in terms of how they provide it because that's a rate limiting step because that will influence to what extent organizations want to provide an alert, and how the alert will function in this system. So a lot of work to be done in that regard.

DR. TRONTELL: Did you want to complete your question?

MR. TUCKER: I have another question actually. Ed Tucker still with Bayer. At least I think. The second

question I have was for my colleague from Europe actually. You mentioned about writing a risk management plan. And if it didn't prove effective, then you would then have an evaluation period, and then you'd have additional measures within the original document. What is the ramifications for not committing yourself to doing those measures in the first place? In other words, you're sort of saying, well, I'm going to write a plan. I'll do half the things now. If that doesn't work, I'll do the other half later. But the ramifications for us in the industry are that plaintiff lawyers tend to look at those types of documents. So when one is committing themselves to say maybe if this doesn't work, then we'll do the next piece. But that really plays into the hands of some of our legal colleagues. And I just wanted from a liability point of view where we stand as industry physicians.

DR. LUMPKIN: Well, it's great you're asking me as I'm neither a European nor a liability lawyer, so I'm

clearly the last person –-

MR. TUCKER: My apologies.

DR. LUMPKIN: –- to answer it. You know, I think you raise a valid point on that. You know, we tend to look at the idea here that it's a prospective thought process. You are looking at what you think the risks are, how to best approach it, and how you're going to assess whether indeed you've done that.

You know, as far as what I've seen and in talking with my European colleagues, I don't think they're expecting a detailed second plan, but really more of the assessment and when, and then what alternatives might exist at that point. Because I mean the idea is if you've got something that requires a risk minimization plan, it's obviously falling into that 10 percent. If it doesn't work, the alternative is to remove the product. And so the basic question is can you still come up, can you still imagine a positive benefit to risk perspective on this

product, you know. And to me, it seems like that's a very legitimate thing. As you say, anything can play into the hands of a liability lawyer, but part of what you're doing here I think is your case is we're trying to be responsible, prospective, thinkers as to the life cycle of our product. And trying to make the best data driven case that it has a positive benefit to risk profile.

DR. TRONTELL: Thank you. Let's thank our speakers again. And I think part of the reason we're so lucky having many of you still in attendance is that we told you that Hugh Tilson would be helping us in the wrap-up. So Hugh, would you like to have the chairs here at the front of the room?

DR. TILSON: Yes, please. Chairs, come on up. As long as I get the last word, you're welcome to join me. What can I say? Nice to see you all. Nice to see so many of you still here.

I have a couple of assurances that I would like

to give you. One of them is that I will talk equally rapidly as I did this morning. Second, I won't say the same thing primarily because I can't remember it. Third, don't be too nervous that I'm going to quote you directly because we don't have a lot of time, and so there are only one or two quotes sprinkled throughout what I have to say. And fourth, as I say, this session is for you.

Here's my suggestion about what we ought to do here. First, I'm an epidemiologist. That's a confession, but in 2007 with the Congress now implementing so-called FDA re-invention or rediscovery or re-vitalization or as is it re-vivification or re-vivisection? It is clear that epidemiology has been mentioned in the annals of Congress and the halls of Congress more in the last six months than ever in my 25 years in the pharmaceutical world. Just remarkable that they have discovered pharmaco-epidemiology. That's the good news.

The bad news is there aren't very many of us.

So we are going to be scarce commodities to you all. Nonetheless, I am an epidemiologist, and I would like to say that you never have a classification scheme or session that doesn't have a final panel, that is everything that we didn't talk about in the other panels. And so that is this panel, the panel of other.

I read some cross-cutting issues that I heard in the first day. I'd like to read out some amendments that I've made having heard today, a remarkable and very thoughtful day.

I ran into some challenges for this afternoon's panel earlier today. I'd like to re-challenge the panel now with some specific challenges. But if this isn't for you, then I think you're not going to get your maximum mileage out of the last couple of days either. So own this session, would you? What I plan to do is to lay out issues that I've heard and action recommendations which I have heard from you. What I didn't hear was a lot of

ownership of the action. It was a lot of they might, or why doesn't someone. So now it is why don't I, or if not I, then who might do some of these things? Not Hugh, who might do some of these things. So own some of these recommendations.

Now I will say as I go through this that the recommendations that I heard were complimented by the Subway sandwich for snacks group over lunch, the panel, who all got together over at Gourmet Lunch in Room 1111. And they heard a lot of action recommendations too. So I'm also going to repeat what they would have said had they given a full speech. But they're not going to give this talk. Rather, they're just going to respond. They're going to say, yeah, that's what –- but how about this, and maybe a little additional here. So we're going to go through the action agenda, go to the panel, see if there's anything on the action agenda that need to be there, then go to you, see if there's anything on the

action agenda that need to be there. And then the tasking, that is to say, and if they are and they belong there, then who ought to do them. All of that, I can promise you before 5 o'clock. I mean those of you who know me know that I am nothing if not eager to get the heck out of here.

So here are a few cross-cutting issues. Remember I started off the day by saying there appears to be consensus that we agree on the objectives, although they need some clarification, but we're not sure we agree on the methods. Well, at the end of the day, I think we're still there. Everybody knows that we want safe patients to get the right drug and the right patient at the right time. We don't want barriers to access to drugs the patients need, but we don't want drugs that are excessively risky given to persons who do not need them, or will not gain the benefit. And we want to balance the benefit against the risks. So that's clear. Everyone

agrees on this objectives. It was wonderful to hear those repeated again and again. I suspect that you could probably have done so and even more rapidly than I just did.

And there's consensus that we better stop bickering and move forward together. This has got to happen. Didn't you love the response from one of our distinguished industry regulatory affairs panelists from the microphone who got up and asked have we changed the way we talk to marketing. And said, "If you don't understand the need to manage risks, you might not be in the right industry." I mean that's a see change, and it's wonderful and we are there.

Standardization. Well, I said each RiskMAP is unique, but the systems in which they are inserted require standard approaches, so how do you adjust those. And we heard, included in these last couple of panels, some wonderful and promising approaches. No more –- remember

when we were talking about the early no-blood, no-drug risk management programs putting them together working without a net, or doing so for Accutane. Well, now we're not working without a net anymore. There is a net out there. The question is whether we can achieve net benefit of that experience.

Transparency. Well, I said this morning adoption requires acceptance, acceptance requires understanding, but the sector requires intellectual property protection and is yet to develop effective communication around this issue. And I think that is still my conclusion, but today has shown me a series of very promising communications strategies and resources and approaches, including at the agency. And knowledge transfer is also very promising. So there are some ways forward there as well.

Regarding empowerment. This morning I said management requires control, but professionalism requires

flexibility. Regulation is central, implementation is localized. I still heard a lot of that structured strain, but I think there are some great opportunities to bridge that gap. And we heard several ideas today. So let's see if we can come up with some action items here about how to bridge the gap between local and central, government and practice, regulation and flexibility.

Regarding resources, specialized processes increase costs. But the (indiscernible) cost containment, there's a strain, but we heard a lot of other things today. I loved the human resources needed for this, again epidemiologist full employment act of 2007, and the wonderful pharmacovigilance experience describing risk aversion epidemiologists as those who act like Superman standing on top of the kiosk in responding to a thousand calls a day.

Evidence. Well, risk management isn't intervention. Interventions are therapy too and require

the same ethics and proofs. And we heard some great conversations about ethics, particularly Brian Strom's ethical quandaries, particularly when we don't know quite what the question is and have the obligation to be sure that we think as public health person, not just individual therapists, particularly in the area of risk management.

And then finally a new cross-cutting issue that emerged from today's conversation, and that is this whole question of an incompletely gelled policy. We're still in the (indiscernible) policy relating to RiskMAPs. We need continuing consideration of these issues, and a bunch of them came up today. Equity, access, cleaner criteria, thresholds, end points. Do we ever end the risk management program. Unintended consequences, and the rules of ethics. Those are all out there today, and I think that was just remarkable.

So here's the challenge to the final panel. It was so given that. You listen and did you hear actionable

steps. And here riskmapping is what we're going to be doing now, the way forward.

Over lunch, we brainstormed a series of these. And I'll just go through them briefly, then ask the panel to comment, then ask you to comment. FDA has to make some changes. Some are underway. You may want to comment on them from the floor, particularly like Mac Lumpkin speaking to Europe because he's not European. Please speak to FDA if you're not an FDAer. Informatics. The last panel was just full of opportunities, shall we say, or challenges caused by informatics. A bunch of them were in our noonday brainstorming as well. Unfortunately I was sitting over there with my computer.

Now the whole question of effectiveness and benefits, RiskMAP methods, and then keeping the torch burning. So let me go through these actionable steps quickly. First, enhance FDA functions. "I'm from the Office of Neuro-Pharm problems –- programs. Whatever I

am, I'm here to help you." We hear the suggestion that FDA needs a go-to person for risk management. We heard that "FDA must develop consistent standards rather than one off and ad (indiscernible)." Without asking –- suffering from the genie's curse of getting something you wish you hadn't wished for. So what those ought to look like and how did it get developed critical.

Transparency is certainly necessary in these processes. There needs to be better access to information, a list of drugs that have med guides, a list of drugs that have risk management programs, maybe even a standard list of components of risk management to programs and their progress. IOM has recommended similar such lists for other post-marketing mandates. Why not for this?

The agency needs to be able to be nimble and quickly responsive to changes in risk management programs when they would be learning as they go above the –- from

the high flying swing over the net, particularly for continuous process improvement as we learned from Gary Slatko's excellent public testimony today.

We certainly need more effective risk communication. Let's hear it for Paul Seligman and this new office. It's just great that we're doing that, but we don't quite know how to do it. So there's a work plan there I know. And also how to talk about risk in the context of benefit. And then maybe there needs to be a RiskMAP policy office. Maybe it's a go-to person, maybe it's in Mac Lumpkin's office –- it's somewhere –- that actually begins to prosecute these policy issues and provide oversight to this process. A final common pathway. You like that, FDA?

Let me go through the Informatics agenda here that I heard. Great talks, particularly the last time, about clinical decisions, support systems. No surprise to you, I know, that this is an area where there is a huge

research agenda. Fine for us to talk about making more interesting prompts, but how do we do that, getting people's attentions? You can't have a world class expert ever stand before you again and say these problems are boring, and we heard it today. So how do we get beyond that? Well, this is an action agenda item.

The large databases are extraordinarily promising, and I loved the Kaiser presentation for that reason and for many others, being a Portlander myself. And for sector monitoring exposure, outcomes, utilization, off label use, off program use. But we also heard that sometimes this door is closed if the people whose data you're monitoring don't use your drug. So there are some disconnects here between this wonderful world and RiskMAPs that probably can be better bridged with better access to broader data sets, including those for third party payer systems beyond HMO's.

Web-based communications, another action agenda.

Everybody said we need to be in touch with one another. Could there be chat rooms, could there be a central repository, a clearinghouse where we do for clinical practice guidelines. If so, what would that look like? And knowledge management, including managing with hot links. Sometimes that's a problem, particularly between government and industry, but something that the CERTs might be able to contribute to. For example, and being sure that if there is a resource out there, and you don't know where to go, there is a go-to place and it's electronic for those who have cyber facility.

And then finally some extraordinary corridor conversations about the dilemma of asking the computer to do too much and forgetting that the computer is an adjunct tune not a substitute for humans. So being sure that as we move forward here, we don't forget that sometimes the best practice is when the doctor and the pharmacist actually talk and talk through a problem, not just

exchanging bitter e-mails.

Third, actionable set of steps has to do with this question of it's the benefits, stupid. I mean we have, with regard to the benefit to risk balance, a huge methodologic challenge. It's fine for us to say we need to do –- we don't know how do it. So there's a research agenda there. We need think-tanks, consensus conferences, capturing best practices. We need to remember what CMS learned and said internationally about benefit to risk balance and how to talk about it, which is we don't know how to do it, and we don't know how to talk about it. But on the other hand, it must be ever before us.

And there are other benefit issues. There are methodologic questions. There are communication questions, and the whole world of effectiveness research. AHRQ is now pioneering with a minuscule budget to do so. So as CMS comes into this process with Medicare drug benefit, surely funding the comparative effectiveness

world will be part of our glorious future.

And then there's the fourth action agenda about RiskMAP methods. I mean you heard about some tools. And you heard about ad hoc evaluations of those tools. But we yet –- we are still far from a tool kit or a tool box. Or even a place where tools can go and –- or where you can go to learn about tools and the extent of their vetting. So to have a credible intermediary –- a game plan here to capture lessons about tools is going to be just critical, of vetting and developing from those best practices. There needs to be good risk management practices. And I would submit that the companies which have suffered from micro-management from the Food and Drug Administration, or at least they reported that they had at this meeting, could have got beyond that had we had good risk management practices in place so that they could refer to those instead of having to work ad hoc. We're a long way from that but maybe not so far. Maybe it's time.

And then the final actionable agenda here is keeping the torch burning. This has been a great meeting. This isn't a hot subject. It is one which is going to be evolving rapidly as Congress learns how to spell pharmaco-epidemiology in the next couple of weeks. And so what do we need to do to keep the torch burning? Well, maybe a web forum, maybe a chat room. Who would convene that? Maybe a safe haven for people to talk about the mistakes they're making, and the fears they have, and the lawsuits they're trying to avoid. Maybe a trusted national resource. Maybe the CERTS. Some trusted national resource that could be the clearinghouse for this work. What about consultants in the field? Have they been vetted? Do you know who the good ones are, the bad ones are? I don't think so. And we need to have some better information about that, or maybe at least in the chat room to share experiences.

And then of course publication, including

publication of the proceedings from today. Sector engagement, both afferent and efferent arms. We talked a lot about that, about how can –- I'm practicing pharmacist. You just asked the egghead at the University of Arizona. Why don't you ask me? I know more about this than he does. Well, all right. And then once we're out there, how do we learn from them about their experience? So some of that. And then what are we going to do specifically to follow these two days?

So there's your action agenda, panel. Did I miss anything? Anything you want off there?

DR. TRONTELL: It's not big enough.

DR. TILSON: It's not big enough, says Ann. You have a microphone in front of you. Anything you want to add –- I mean this was brainstormed by them, and we agreed they would not give speeches about any of these. Nor would they be attributed to any one person. I hope you noticed I didn't blame anyone for this. I didn't give any

direct quotes in that extraordinary think-tank. Anything else on this action agenda before I go to the floor to see if we have heard you and missed some key action agenda items? Be prepared to come to the microphone, folks, if you have some action things you want to recommend. David, I see you moving to the microphone. Anybody from the panel want to chime in?

MS. KWEDER: I'm not sure what you're expecting from the panel, Hugh.

DR. TILSON: Just to see if there's anything missing from this action agenda, or something that you want to specifically say, yeah, that's right on, and we have some ways forward here, Sandy, either one.

MS. KWEDER: Well, I made a list –-

DR. TILSON: (Indiscernible).

MS. KWEDER: It has some of that, which I can share now or wait. Maybe I should wait.

DR. TILSON: Well, no, no. Now's your chance.

If you have some things to add here, and I'll even add them if you want.

MS. KWEDER: Okay. I was able to –- I think from a high level perspective at FDA, there were five major themes here, some of which were better discussed than others and covered other areas. First is the big message that I took away from this is that RiskMAP is a mystery. We don't know what it is. There were a lot of questions about that yesterday, people saying I want to see the RiskMAP. Well, there isn't always a RiskMAP. A RiskMAP is a collection of things. And I think that one of the things that would help us talk about RiskMAPs or REMs as I think the Congress is going to call them is if we were able to put a more consistent definable framework around this thing so that when we said, oh, this is a drug that has a RiskMAP. Everybody says, ah ha, a RiskMAP. Okay. Or whatever it is we're going to call it. What are it's –-

DR. TILSON: Right. And it would be a template. You'd know what one looked like. What –-

DR. KWEDER: What are its components.

DR. TILSON: Sure.

DR. KWEDER: What are the measurements that are part of it, what are its goals. And then –-

DR. TILSON: If I go to the FDA website, I'll be able –-

DRS. KWEDER: Exactly.

DR. TILSON: –- to find their risk plan –-

MS. KWEDER: It should be transparent. It should be publicly available. Everyone ought to be able to understand what it is and why it's there.

Second and similarly it's time for I think the agency to be very systematic in thinking about AHRQ, what the criteria are to have a RiskMAP, and how –- what are the kinds of things that would lead one to need a RiskMAP. You know, we do this in guidances all the time, and we

have some of that in our current guidances, but maybe we need to hone it down into some more simplified systematic ways of thinking about things that could be part of, say, that website.

DR. TILSON: Good.

MS. KWEDER: At the same time, I think systematic does not and should not be robotic. And activities and interventions have to be developed with great care and attention to patient care, and understanding when are efforts to facilitate patient safety are actually interfering with meaningful patient access to medications. And I think we heard some examples of that. You know, I think yesterday that the docs that dry-lab the data because they're so frustrated by how onerous the data collection aspects are that they have to do that in order to get their patient the drug.

As far as being systematic, we also need systematic tools to help us assess some of the components

of RiskMAPs. We don't really –- as we're developing –- we're just beginning along this road and we have some tools that have been started to be employed in a lot of these programs, but are they doing what we really want them to do and how do we test that is still a big question for us. And we have to have that as part of the components of any RiskMAP that gets put out and implemented.

Third, in terms of being systematic, FDA needs to be more systematic in the way we evaluate and decide about RiskMAPs. We don't have a central location for RiskMAPs. We have a very, very small staff that gets –- that weighs in on them, and they do a phenomenal job. But that's just not enough people. And it's people who are involved in the business of reviewing drugs are in a completely different mindset than people who are actually using the drugs and have to think about how to interface safety and efficacy data with standard clinical practice.

We need to get better at that, and we need to put resources and processes and have a –- it's your comment about a go-to place that oversees this.

And I guess –- I think that –- one of the things that I think needs a lot more discussion is –- I think this is my number four –- we have to start thinking about RiskMAPs with the end in mind. And a lot of this comes down to some real philosophic decisions about what is the role of the FDA in requiring these RiskMAPs. What are we? Are we keeping patients safe? And if we are keeping patients safe, in what way? Are we the keepers of the public? And at what point are we putting in place a system with computer tools that stops people from thinking? And that came up in the last panel. We don't want doctors not to think because they're relying on a computerized risk management program when the computer can't think of everything. You know, some of –- I've heard it said, you know, by some at FDA that we're the

nation's doctors. I am not the nation's doctor. And heaven forbid, I don't want the FDA to be my –- in a RiskMAP to be my doctor. I want doctors to be able to have tools that help them take care of patients. I want my doctor to have everything he or she needs to help me use the medicine wisely. And we need to make sure that we're thinking about that. And that gets to my question about when are we done, when have we established a sound practice that's part of, you know, expectations in the community of practitioners such that we don't need hard key entries to keep people in line. When can we make a shift.

And then my final comment that, Hugh, you made a comment –- you alluded to and came up in –- in our very interesting industry panel today. It was really encouraging to hear from the companies that presented about the importance of risk management and safety in their corporate cultures. I don't believe that that's why

it spread. And I want to see that –- I'd like to see us really having some hard discussions about all the difficulty of making that part of corporate culture in the industry.

You know, I said at –- I think one of the struggles that we have is that when, you know, in a room like this where there a people from the industry present and working on these really hard risk management problems, we usually agree, you know, all the parties usually agree on what needs to be done. And then what happens is everything gets turned over to marketing. And all the hard work of planning and assessing safety and understanding the risks and putting together even the best package insert you could ever imagine gets undone by a marketing program. And that really –- that's a shift that has to occur for some of these products.

So, you know, at risk of being crucified by my colleagues, I'll stop and see if anybody else has anything

they want to add.

DR. TILSON: I think your colleagues aren't going to crucify you. I think that what you did was to elaborate actually on the policy and practice agenda that they came up with over lunch. I mean let's just go back and look at this action agenda. I think it's the same. There it is on the screen. We need a go-to person --

MS. KWEDER: Oh, I couldn't see that. I hope I wasn't redundant.

DR. TILSON: No, you were reinforcing. That's not the same as redundant. Transparency and access. Nimbleness and responsiveness. More effective communication and RiskMAP policy and oversight. The agency has to take that role. And your notion about the end game also came up and is there as part of the risk management agenda, or research agenda. There has to be a way for us to figure out what the goal is. Excellent summary. I'm thrilled that you went there at lunch

because it's nice to have what came out of lunch validated. Anything else from the panel before we go to the audience about what's on this agenda? If not, David? Oh, I'm sorry. Ann, get your mike.

DR. TRONTELL: It may be that you are speaking more quickly than I could hear. I actually think there's one thing that maybe I need to put it more in simple terms that I can understand is connection. Part of the purpose of convening this group and in part some of the connection that I think AHRQ and FDA attempted to model in bringing this meeting together, which is in fact the stakeholders that meet here, and perhaps this is pushing it back out to the audience, need to connect with each of these agencies, as well as with each other. Some of this I hope has already happened in the course of today's meeting. And I promise I won't hum kumbyjah, even though it's the end of the day. But I think –- I do think there is some sense that we are in this together and need to behave

appropriately, particularly as we think of next steps, how and who among us might be best able to convene a follow on to what we've started in these last two days.

DR. TILSON: I love it, and this graphic is one of my favorite kumbajai graphics anyway when we have the globe and people joining arms around the globe. Sandy?

MS. KWEDER: Yeah, I certainly echo what Ann says, and I only spoke for FDA, but there's no question that we can't do this all alone. You know, just the tools that are needed to do a lot of these systematic evaluations, we're not experts on those. And we need agencies like AHRQ and other experts in the community to help us with that.

One of the things that –- two follow-on points, the nimbleness and flexibility. I think that really comes down to staffing. When you only have a couple of people who are really working on these, you can't evaluate and think in real time and facilitate making changes.

And secondly, one of the struggles that we've had, if we look back over the programs that have been developed in this area in recent years, the RiskMAPs that we do have, many of them have been developed in a time of urgent need. And so I think where we have not done well in engaging particularly patient communities and provider communities in building the programs in a way that facilitates good care, maybe because they have been developed in, you know, with a sense of urgency that maybe there wasn't time. I think that's a mistake at something we'd really like to avoid. That's why we have already included –- I can share with this audience, it's a much longer discussion, but we're in the process of implementing some significant changes in how we go about the process of reviewing NDA's and BLA's. It's in response to a good review management practices. And focused attention on whether a product is going to need a risk management –- a RiskMAP, a risk management plan will

come very early in the development process as part of this. And I think hopefully that'll help us avoid some of the crunch time that leads to sub-optimal programs.

DR. TILSON: That's terribly important, and I think you may have been out of the room today when several of the speakers, particularly describing the risk management programs, said that one of the problems was that they operated in a spirit of continuous quality improvement because they knew that they didn't know quite what to do, so they did things, then they had to propose changes. And they did have problems getting nimble responses from the agency. So I take it you hear them.

MS. KWEDER: Right. And in fact, I can give you a great example is, you know, in a program like –- we're evaluating a risk management program now that has about a year's worth of data. And it's really going to take us, you know –- companies and the program have done a great job trying to pull together the data, but it's

complicated. It's sort of messy. It's because it's about people. And it's going to take us months, a couple of months to really look at that data in the kind of detail we like to look at it in. So then it'll likely be another couple of months before we can propose specifics –-

DR. TILSON: So is that person months? And if there were persons, would it take those months?

MS. KWEDER: Exactly. It would take us fewer months.

DR. TILSON: That's what I thought. Anything else then from the panel to add to this aggressive agenda that you all laid out over lunch? John?

DR. GARDNER: Can I just add one thing? I'm John Gardner, and I'm sitting in for David Meyers, who we worked with to plan the provider-payer panel. And I'm kind of a poor man to substitute for the care of that panel. But I come from a background of –- a long background of injury epidemiology. And I think the point

we’re putting here is really engineering controls or what’s working. And behavioral controls usually don’t work. And a good example is hearing loss from noisy machinery. And you can tell people to wear ear plugs as a start. And then that doesn’t work, and so then you buy them ear plugs and hand them to them. And that works a little better but not much. And then you can put up signs at the entry that says put your earplugs in before you enter the door. And that works a little better, but then you can put a sentry at the door who says you can’t enter without earplugs. And that works even better. But what really works is redesigning the machinery and encasing it so that people can get near to it without having to wear earplugs. And then you’ve taken out the behavioral component. And I think that’s the issue here is with RiskMAPs is trying to move further toward engineering controls and further away from the behavioral controls which simply don’t work in many circumstances.

DR. TILSON: Yeah. You know, we teach that to everybody at the school of public health, is getting an MPH, teach them the three E's, that is to say it's not just engineering, it's not just education, it's not just enforcement. In fact, to make it work, you need all three. David, at last. Reintroduce yourself, would you?

MR. LILIENFELD: I'm David Lilienfeld, Fibrogen. And like Ed, I'm still at Fibergen. My pleasure. Two things. One is something I think, Hugh, that you may have alluded to but you didn't hit dead on as much I thought you were going to. And that is the notion of training, not so much in terms of just numbers but content. It's not clear that what academia is interested in training is necessarily what the industry requires and is interested in hiring. Or for that matter, what the regulators are expecting to be interacting with as they review programs and have their expectations for where the programs are going to go. So I think it may be time.

Perhaps this is something for the CERTS to take the lead on to sit down and begin a discussion of what is in fact the way to train a risk manager because it's not clear that it should be just a pharmaco-vigilante that's retooled as it were. In fact pharmaco-vigilante may be the worse thing to start with, and that's a discussion that hasn't even really begun yet.

Second thing is going back to the idea of a forum, I think one of the things that is very, very important about this meeting is that it provided a wonderful forum for interactions. And I think that we've haven't had enough of those, even though we've had quite a number over the last 10 years. But I think it's very clear, at least from the conversations I've heard in the last few days, that it will be great to have more of them. And I know they take an awful lot of work to put together, and the fact that this one has been as good as it is reflective of the hard work that was done in it's

planning. And I think that we owe a debt of gratitude to the folks who took on that hard work. Because I don't think it's really been given the recognition that it's really due.

Having said that, there are virtual forms that can be put together that were alluded to. But it would also be nice to have perhaps at least some of those forms coming out to the west coast where there's a burgeoning biotech industry in south San Francisco on the peninsula. I guarantee you in February, it's nice and warm. You don't have to shovel snow, so on and so forth. And it will provide an ability to introduce of our managements to these ideas in ways that they do not have available to them now. And I think if that dialogue began, it'd be very helpful for everybody, including those of us in the safety departments.

DR. TILSON: It's such a wonderful point, David, I'm going to memorialize it in a slide while the next

gentleman comes up to the microphone. And you actually made three quick points. Let me just be sure I've got them. The first is we don't have a pharmaco-epidemiology workforce to implement the pharmaco-epidemiology full employment act of 2007. We have to have one.

Second, to train them, we're going to have to have competencies, curricula, and setters. Maybe the CERTS can take it on, but not without resources, and we're not resourced for that workforce agenda activity. I've actually had the privilege in a prior setting of calling this to the attention of the Office of the Commissioner and the commissioner is very well aware of this, probably more so than anyone else because he can't find employees trained for his own epidemiology needs, and they are a small portion of the sectors. So we're going to have to do something about that. Thank you for that.

And then third, of course, it is a nation that has that wonderful west coast, particularly I'm fond of

the west coast of Kona and Maui. There are lots of west coasts we could go to. Next speaker, please.

MR. MAKOWKA: Yes, Ken Makowka. I'm a patient consultant for the FDA as well as a myeloma patient. I learned a lot in the last two days. I totally understand the need for the RiskMAPs, but I keep hearing about funding, and I know where the FDA gets its money. Is anybody in this room from Congress? Is anyone here finding out where the money –- the need for the money?

DR. TILSON: The answer to that is of course, no, there isn't someone here from Congress.

MR. MAKOWSKA: May I ask why?

DR. TILSON: Would you like to answer your own question? And then I'm going to go back to the slide show. But your point is so brilliant that we need to talk a little bit about it. And it's a great segway to the next portion of this session anyway, so let me do that and take advantage of your terrific point.

So if we agree that these are the action agenda items with the one that you added Sandy, and the one that you added, David Lilienfeld, then the question is who on earth is going to do this. So great point, great segway. And here's my list, and you see Congress is on the list, of key actors that we need to have involved. And many of them were here at least with representatives but not necessarily the right representatives or representatives who can deliver their constituencies, people speaking about the issues.

But if we're going to pull this off, Sandy is quite right. This is not the FDA's job. This is everybody's job. FDA's on the list and (indiscernible) at the top. AHRQ is there because we know that AHRQ is the public health arm and the health services and health systems and the research arm of the FDA and the implementer of the FDA Modernization Act of 1997 through the CERTS by legislation. Obviously they're there, but

other government agencies, the VA, the Department of Defense, the CMS, and of course NIH can fund some of this stuff too.

Now sponsors and industry, particularly in the workforce issue, industry has taken the lead in the absence of public funding for training of pharmaco-epidemiologists but maybe not enough, and maybe not in the right way. And certainly not in a concerted way. Providers and professional societies owning these agendas, perhaps coming up with consolidated approaches. Trade associations, we heard from yesterday. Patient groups, including your wonderful representation. Thanks for doing all you do to be sure that people don't look at the patient as the bottom of the food chain, I believe was your term of phrase.

Another key stakeholder too, being the epidemiologists, and of course, I'm an academic from the CERTS, and so I believe that the CERTS can take on some of

this as well and Congress. And of course, you. So let's now have some bidding for some of these tasks. FDA wants to take on its task I know. And you've already heard Sandy talk about some. Anything else you want to talk about taking on representatives from FDA?

DR. DALPAN: Yes. I'm Gerald Dalpan, director of the Office of Surveillance and Epidemiology, FDA. I think there's a lot we have to do. I'm not going to give an exhaustive list because it'd be very big. I think a few areas that are –- one is the evaluation of these risk management plans. This is clearly an area where we have to grow. Our staff for this has been very small. We're growing slowly and we hope to grow more, but clearly evaluating the plans as a whole, and then the individual component tools of those plans, and then evaluating tools, a common tool across many plans to see how effective that tool is. And I think only then can we start making the kind of, you know, rational, intelligent evidence based

decisions about how to build a RiskMAP, or how to evaluate it.

DR. TILSON: Would you see yourselves working in isolation, or would you see yourselves partnering with some groups to put together those evaluations, Gerald?

DR. DALPAN: Yeah –-

DR. TILSON: And do we have the methods to do this yet, or do we need some methodologists at the table?

DR. DALPAN: I suspect we need a lot of methods development here. I mean this isn't straight epidemiology, straight pharmaco-epidemiology. It involves other things. It involves elements of how people understand the communications given to them. That's another big area I think where we have to do a lot of work, and that's in risk communication. So I can imagine other areas, like human factors analysis, failure mode effects analysis, things like that. The systems here are so complex that I don't think this is a single discipline

issue. And we're going to have to expand beyond our traditional medical epidemiology I think to get involved in that.

DR. TILSON: I was thrilled to see Paul Seligman walk back in the room because I extolled his virtues in his absence. He actually, as you know, ascribed much of our progress to a series of partnerships getting to FDA's risk management position, including the CERTS, think-tanks and some CERTS methodology work already in the field. And I suspect that he would be happy to embrace a member of the steering committee, seeing that continue. And in his new role in risk communication, one of the most important CERTS think-tanks we had was on the unfinished business of understanding the science of risk communication. So there's a lot of trial and error and learning that we need to do there through some disciplines. We haven't engaged well either. And I understand from informal talks with him that FDA likewise is engaging other external partners

to think those challenges through too.

DR. DALPAN: I think for some of what they call quick wings. I think one of the things we'd like to do would be to get a website up that explains risk management programs and what those programs are.

DR. TILSON: You bet.

DR. DALPAN: We do have med guides on our website. It's virtually impossible to find, but they're there. There's a list of all med guides. I couldn't even tell you right now how to get there, but it's not intuitive or easy.

VOICE: Go to FDA --

DR. DALPAN: (Indiscernible).

VOICE: Paul's trying to find the list now.

DR. DALPAN: From the Cedar home page, you go to the drug information pathfinder, and you'll find it on the next screen somewhere. Can I just add, though, another point here?

DR. TILSON: You better.

DR. DALPAN: And I'm from the Office of Compliance. And we focus of course on industry compliance with their obligations. And I kind of summarized the industry obligations when they decided to market a drug as the three M's, manufacturing, marketing and monitoring. So they need to manufacture their drug perfectly. They need to market it appropriately to make sure it gets used for the maximum benefit at minimum risk. And they need to monitor the quality of their product, the use of their product, the adverse events related to their product, and the risk management programs that are implemented through that. And I think it really is the obligation of those who are making money selling the drug to make sure that that drug is used appropriately, and that they maintain the quality assurance. And FDA really can't be the quality assurance for each company. We can't go in and do our inspections and become their quality assurance

program. We have to –- the companies have to have their own quality assurance, and we can audit their quality assurance and say, yes, it's good and we won't worry so much about you. Or we could say, no, it's not good, and you have to fix it. But it really has to fall on again on those who are making money by selling these drugs to assure that everything they do is top quality and of maximum benefit with minimum risk.

DR. TILSON: That is such a marvelous point. You know that out of one of the CERTS think-tanks on risk management, there came the realization that we didn't know what the level of effort in industry was. I mean your point was a good one in that they own the drugs and they do the work, but we didn't know how much they did. And so actually a survey was commissioned. PhRMA helped to fund it to see just how much industry was currently spending on the three M's, or on the third M, on the monitoring, including epidemiology. So it turns out the median spend

from a company exceeded the entirety of FDA's spend on drug safety. So it's a terribly important point and well made, and one that we need to understand as we look at the drug safety system and try to see whose role is which within the partners. Somebody from industry had a microphone. David?

MR. LILIENFELD: I think it's important to remember that, you know, we don't have to reinvent the wheel. A lot – (indiscernible due to poor audio.) If you go back to 1940, '50's and '60's, there was a whole area of epidemiologic work that dealt with program evaluation. And you can look at the health service research that grew out of that effort. There are folks like Bob Brook, for example, who's been around who can be very helpful in terms of how you go about looking at a RiskMAP and evaluating it. They've done it (indiscernible). They've done it in economic (indiscernible). But it's really not that different than going and putting it into the

construct of new adverse events instead of looking at dollars, (indiscernible) and the same effort.

DR. TILSON: And how appropriate that you'd bring him and that discipline up in this building because of course, AHRQ was part of the –- and the agency (indiscernible) research policy before that were part of the making of Bob Brook and this whole body of scholarship. So a good tribute to the FDA-AHRQ partnership. Thanks, David.

Well, we know you, but you should still probably come up and introduce yourself again. Welcome back to the microphone.

MS. BLACKWELL: Mary Blackwell. I'm pediatrics and health services at Boston University School of Medicine, School of Public Health and multiple sclerosis patient receiving Tysabri, benefiting from Tysabri. Wouldn't be standing here today without Tysabri.

Having spent a lifetime in medical education,

the point about having your systems not remove the thought process from doctors, I get back to how we educate physicians. And the physicians I see in training all the way through, you know, can almost be divided into two categories, you know. And they are a personal temperament thing almost. Those who relish being allowed to think about what the best thing to do is. And those who would actually prefer to simply be told what the safe thing to do is, the thing that's going to keep their patient and also them out of trouble.

And you need to think about sort of the vast variety of people who end up practicing medicine. And some of the drugs we're talking about are largely in very sub-specialized practice hands, which tend to be the –- to attract the thinkers, but not all. And I think you have to keep that in mind in terms of –- we have to keep in mind of how we're training physicians to think and to look at their careers as a life-long learning that they have to

adapt and that there's no recipe.

DR. TILSON: Just added it to the agenda. Of course, it's part of the education agenda as well we must do it, and the CERTS are working on that. The CERTS are actually working on a curriculum to improve therapeutics particularly. But that's a subset of what you're talking about because you're talking about how physicians –-

MS. BLACKWELL: How to do these, you know, alerts and how to do these maps, and how to, you know, make them work for the sort of –-

DR. TILSON: Right.

MS. BLACKWELL: (Inaudible).

DR. TILSON: You've lost your mike again, and I'm going to have to ask you to keep brief because we're almost out of time. Did you have another point you wanted to make?

MS. BLACKWELL: (Inaudible) maybe didn't hear at all was quality (inaudible).

DR. TILSON: No.

MS. BLACKWELL: And I think that that's, you know, (inaudible) assessing the benefit that we talked about (inaudible). And we did talk about the burden on the patient, but I think I didn't really hear the word quality of life (inaudible).

DR. TILSON: It's a critical point and I edited it shorthand to that comment about benefit assessment effectiveness assessment. That's all part, of course, of CERTS comparative effectiveness (indiscernible) and arts as well. Effectiveness is not just changes in measurable patho-physiology.

MS. BLACKWELL: And just lastly, I want to –- I don't understand the lack of funding for (inaudible). I'm sure you don't either. But, you know, the return on the dollar, per dollars spent at NIH has to be (inaudible).

DR. TILSON: We're, of course, not allowed to advocate for more funding in a federal agency while we're

in a federal agency, but let's talk privately here. And I'll be glad to give you a membership form in the Friends of AHRQ. There actually is an organization that's working on exactly that for exactly the reasons you talked about.

MS. BLACKWELL: I'll join.

DR. TILSON: Right. So last comment from the floor. Will, do you speak with an English accent these days?

MR. MAIER: No, no, I still have an American one a little bit. I'm Will Maier. I work at Elan Pharmaceuticals. I'm an epidemiologist. I guess Hugh was mentioning –- I don't actually live in the U.S., but I'm still allowed in, so that's good.

One thing I wanted to try and place on your actionable steps, and I think you sort of alluded to it, and that's how will we weigh benefits against risks in sort of a systematic and transparent way? I mean this has been talked a lot about and obviously Ceom's published a

little book about it and things like that. But that makes a huge difference in terms of trying to understand whether or not one needs a RiskMAP or not. And I was just wondering maybe if people from the FDA or on the panel could comment a little bit about that as well. Thanks.

DR. TILSON: Well, good. Let's let that be the last challenge to the panel. Can we take about effectiveness, and does effectiveness involve quality of life? And then talk about benefit. Can we make progress in that direction? Somebody want to respond? How will we move this forward? I know AHRQ is working on it.

MS. KWEDER: AHRQ is working on it, and so are we. And there is an awful lot of discussion within the agency and between agency and the industry on, you know, better ways to measure benefits, effectiveness, efficacy. We have an enormous amount of work going on right now in the area of quality of life assessments which has much of what is developed in the field of economics does not apply

very well to the human condition. And it's been a tough road, but we are making great strides in bringing the same rigor to those kinds of assessments as we expect from clinical trials and what traditionally has been considered harder measure, you know, hard as in touchable, measures of efficacy. It's extraordinarily important.

And I think it's also important that we learn –- as part of the communications piece that we learn and figure out better ways to explain what benefits patients can expect from their medications. As we all know, every medicine that has been shown to be efficacious doesn't work in every patient. And we don't fully understand why that's the case in helping patients. And practitioners understand what they can expect in the way of benefit. It's not all gloss and glitz. You know, sometimes you're going to try something. It's just not going to work. And you know, maybe you ought to stop it if it's not working. A lot of that is something that we are spending an awful

lot of time thinking about.

DR. TILSON: And AHRQ has a substantial program in effectiveness and comparative effectiveness. Oh, you wanted to comment too? I'm sorry.

VOICE: (Inaudible). Just wanted to add one thing that might (inaudible) Advisory Committee. Many nominations in for that already.

DR. TILSON: And we hope it will be a benefit to Risk Communications Committee.

DR. TRONTELL: Hugh, if I can add just a few words.

DR. TILSON: Ann.

DR. TRONTELL: I think, as you've alluded, I think there's a lot of methodologic work in the area of benefits and risk going on not only with the FDA, also within AHRQ, not just actually within its CERTS program but also within its effective healthcare program and its efforts and comparative effectiveness in trying to

actually put forth some methodologic pieces we hope to actually see later this fall coming from the evidence-based practice centers and also the (indiscernible) network.

But taking a cue from you, Hugh, I think one of the things that I've heard from all of this, at least from the perspective that I might even begin to dare to speak from our AHRQ is making a small problem a bigger one. And I've seen a few things converging here. We have, you know, spirited discussion of additional resources for safety coming from Congress. We have spirited, you know, interest in the appropriate prescribing of medications coming with CMS and the Part D benefit. We have interest in comparative effectiveness and in personalized medicine, RiskMAPs. These are all slightly different ways of doing the same thing as Brian Strom pointed out to us. And I think the opportunities then to combine funding on these different interest areas might really give us the engine

to get what we want done.

DR. TILSON: Great. Get funded and combine it. One last comment from the floor, then we're going to go to the panel for almost last comments, then to me to almost last comments before we turn to you for last comments.

MS. BOUGH: Thank you. I apologize for the last minute note, but I wanted to just add that –-

DR. TILSON: Reintroduce yourself, please?

MS. BOUGH: Oh, Marcie Bough with the American Pharmacists Association. As you move forward with the website that will have a list of the RiskMAP programs and what not, a tool that I think we could all work together to develop that would help practitioners, pharmacists, patients, everyone dealing with RiskMAP programs, would be to a quick checklist that would be available with these programs that could be an easy reference for a checklist of what prescribers need to do, what pharmacists need to do, and then what the patient needs to do, whether it's

registering for a program. If they really do need that sticker, as we move forward just for an easy, quick reference for everyone involved, for the programs that exist now, and then as any new programs develop.

DR. TILSON: That's a neat point. Thanks. And we talked about it over lunch, and whether FDA wanted to put together this website could actually have a template so you could find that information in the same place for each RiskMAP, or if there isn't one, just there isn't one. Work for you? Okay, then panelists, last comments?

DR. DALPAN: You know, there's this area of a lot of growth. I think that –- I hope there's going to be a lot of advances in this in the next several years. Clearly this is an area more than anything else where so many stakeholders are directly affected by the design of the risk management plan. And we were fortunate I think to hear from many of them. And I want to thank all of them as well as the people from the public hearing who

participated because I think this really helpful to me, and I think to our program.

DR. TILSON: Thank you. Any other comments from any of you? John?

MR. GARDNER: I pretty much had my say. Engineering controls, quantitative evaluations, and quality assurance. That's really the key.

DR. TILSON: I love it. Comment? Ann, are you going to be the last comment? Maybe. Huh? What do you think? Well, then let's go to you. Any comments, comments? No? Well, thanks. And I said I get the ultimate comment, and you get the last one, right? Is that fair? I'd like a pen. Oh, yeah. Do you want to –- I was assuming you were read from your cup. Do you want to do that first? And then you can say –- why don't you read from your cup. Then I'll make a comment, then you can say good-bye. Does that sound good?

DR. TRONTELL: It's not tea leaves, but in this

infamous lunch that Hugh refers to, I sought power from caffeine, but it seemed there was actually an interesting message. I'll have to source John Adamski's Starbucks customer from Corvallis Organsis. It says, "Complex problems defy simple solutions." Interesting. A few examples. And then it goes on to say, "We need to commit to a total solution for our perceived problems. We need also to remember that most solutions also hurt people. What or who we hurt and who or what we fix is always the tough part of the equation." She could have just bought a cup of coffee and done something else the last two days.

DR. TILSON: Yeah, if you don't want to come to the follow-up meeting, just go to Starbucks. Let me give you a few variations on the theme of MAP. MAP, making risk management drugs accessible to the right patients. MAP. Making risk management programs acceptable to providers or physicians, since doctors don't like to be called providers. Making risk management programs

affordable to payers and the price weary. Making risk management programs automatable for programmers who want to help in the human partnership. Making risk management programs amenable to privacy. Wonderful set of comments about that concerns and requirements without, on the other hand, forgetting that the public health often requires exemptions from some of those requirements. Making risk management programs articulable to the press. Don't forget the press is part of the public health system. If they get it wrong, we will be harmed. If they get it right, they're an enormously powerful help, particularly bridging the complex techno-speak and the people out there who need to understand what we're talking about. And then finally making risk management programs achievable for that producer and the sponsor of the drug companies, so we've been talking about. They have to be able to do this. And making risk management programs accountable to the public and its lead public health agency in this area,

the Food and Drug Administration. Variations on a theme of MAP.

But of course, my final comment is that this map isn't going to work unless you see yourself on it. Thanks very much. Thanks to the panel.

DR. TRONTELL: Thank you all for a very productive two-day conference. Again a reminder to please give us back these little tags and have a safe trip home. Sandy.

MS. KWEDER: Thank you all. Expect to see you at our next convention, and FDA will be reconvening within the next few weeks. You've given us a lot to think about. Thanks, everyone.

(Off the record - 5:30 p.m.)

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In witness whereof, I have hereunto subscribed my name this 12th day of July, 2007.

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Alma J. Johnson