THE BROOKINGS INSTITUTION

FALK AUDITORIUM

STATE OF BIOMEDICAL INNOVATION CONFERENCE

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PARTICIPANTS:

Welcome:

ALICE M. RIVLIN
Leonard D. Schaeffer Chair in Health Policy Studies and Director, Engelberg Center for Health Care Reform
Senior Fellow, Economic Studies

Opening Comments:

MARK B. MCCLELLAN
Director, Health Care Innovation and Value Initiative
Senior Fellow, Economic Studies

EMERGING ISSUES AND POLICY PRIORITIES IN 2015

Moderator:

MARK B. MCCLELLAN
Director, Health Care Innovation and Value Initiative
Senior Fellow, Economic Studies

Panelists:

JEFF ALLEN
Executive Director
Friends of Cancer Research

BILL CHIN
Executive Vice President, Science and Regulatory Advocacy, Pharmaceutical Research and Manufacturers of America (PhRMA)

PAMELA MCINNES

Deputy Director, National Center for Advancing Translational Sciences
National Institutes of Health

PAMELA TENAERTS
Executive Director
Clinical Trials Transformation Initiative

TRACKING INNOVATION AND MEASURING POLICY SUCCESS

Moderator:

GREGORY W. DANIEL
Managing Director for Evidence Development & Innovation, Engelberg Center for Health Care Reform
Fellow, Economic Studies

Panelists:

MURRAY AITKEN
Senior Vice President
IMS Health
Executive Director
IMS Institute for Healthcare Informatics

JONATHAN LEFF
Partner
Deerfield Management
Chairman
Deerfield Institute

PETER NEUMANN
Professor of Medicine, Sackler School of Graduate Biomedical Sciences
Tufts University

MARTA WOSINSKA
Director of Economics Staff, Office of Strategic Programs, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Summary and Closing Remarks:

MARK B. MCCLELLAN
Director, Health Care Innovation and Value Initiative
Senior Fellow, Economic Studies

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P R O C E E D I N G S

MS. RIVLIN: (in progress) -- for Brookings on behalf of the Economic Studies program, which we're part of, and especially on behalf of the Engelberg Center.

We have a lot of things going on at the Engelberg Center. We talk about serious stuff, like payment reform and how to finance Medicare and Medicaid and a lot of stuff like that, which is very important. But the really exciting things that are going to determine what healthcare is like in a few years are what you're going to talk about here today. It is innovation in many dimensions; how do we do it? How do we make it useful?

And so, I think this will be an exciting day. We've got a very good lineup, and I don't want to take up any more of your time. Let me turn it over to Mark McClellan.

(Break in recording)

MR. MCCLELLAN: Thanks, Alice, very much for that introduction. I'd like to welcome all of you who are here with us in the room and all of you who are joining us online for this morning's event on the state of biomedical innovation.

This is the 2015 edition of our biomedical innovation conference. Today's conference is part of a broad series of Brookings events, both here in -- both on the broad range of issues related by medical innovation and specific topics. As Alice mentioned, this is a critical area for healthcare policy.

Biomedical innovation has a tremendous impact on the lives of Americans and people all around the world today, with over 700 drugs and biologics and thousands of medical devices and diagnostics and development, the potential for longer and better lives in the future is great. But the process of translating good ideas from basic science into safe and effective treatments that can improve people's lives can be long and difficult and uncertain. And the impact of new medical technologies on

healthcare costs also remains a major concern.

So, to speed innovation and to maximize the value of innovation, our conferences and expert workshops have addressed a wide range of issues that affect drug device development. These include topics like clinical trial design, expedited regulatory review pathways like the breakthrough designation, patient access to treatments in development, new reimbursement models intended to promote high value innovation.

But in addition to these specific topics, we've also periodically taken a big step back to reflect on the overall state of biomedical innovation and the most important opportunities to improve it. And that's what we're doing with today's conference; reflecting where we stand and where we're headed, and successfully moving valuable new treatments from scientific discovery to access to patients who need them.

Where have we made progress in recent years, and what can we learn from the recent developments in biomedical innovation? What are the most pressing challenges facing innovation in 2015? And what are the most important policy opportunities to accelerate progress that Congress, federal agencies and the broader stakeholder community and undertake?

We're pleased to be joined for this conference today by leading experts in government, academia, industry and patient advocacy groups for a productive exchange on these issues. We've got two major sessions in our conference. The first is an overview on recent trends in biomedical innovation and insights about important issues in biomedical innovations from a range of perspectives, including patient advocates, governor leaders and private sector and academic leaders.

Second, in the next session, we'll review some of the latest evidence on trends in biomedical innovation, along with how we can do a better job using that evidence to track innovation, to identify problems and promising developments, and to evaluate the impact of policy reforms and other steps intending to improve access to

valuable new medical technologies.

Before we get started, I just want to mention a few of our logistical issues. Today's even is public. Press are present. The event is being live webcast and recorded, so everything here today is on the record. For those of us who are joining online, slides are available as a PDF on the upper right hand side of your screen. And if you'd like to revisit any part of our discussion today, this event will be archived in its entirety on the Brookings web site.

For the panelists in our second session, I want you to meet Serena Coates. Serena, say hi -- up there in the front. She'll help us stay on schedule during that discussion, and we're going to have -- for all of you who are here in the room, we're going to have opportunities to ask questions during each session. If you have a question, we'll bring a microphone over to you to make sure everyone in the room and online can hear your question.

So, just to help us frame today a bit, I'd like to briefly highlight a few of the emerging issues in biomedical innovation that will come up in our discussions today. There is a lot going on in terms of biomedical innovation policy. The House and Senate are both undertaking bipartisan legislative processes or improving the research, development and regulatory review process.

The administration has proposed new biomedical research and development initiatives. Federal agencies are undertaking new initiatives related to fostering scientist advancement and promoting access to more effective and safer treatments. But I don't want to put too much emphasis on what is happening in the public policy area alone.

One of the most notable trends in recent years, which I'm sure we'll discuss today, has involved more efforts led by patients and the broader stakeholder community to accelerate progress and access to innovative, valuable treatments. Creating opportunities for progress through public, private collaboration is becoming an

increasingly important feature of biomedical innovation.

So, just to go over some of these pieces, since last year, the Energy and Commerce Committee of the House of Representatives, as many of you know, has been pursuing the 21st Cures Initiative. After almost a year of hearings, white papers, many efforts at stakeholder engagement and other steps, the committee released almost 400 pages of legislative proposals earlier this year.

The proposals cover a broad range of topics, such as possible pathways for expediting clinical development and FDA regulatory review and initiatives to promote the development and use of better clinical and outcomes data throughout the life cycle of a product, and addressing some potential structural barriers to coverage of new medical technologies.

Also notable in this effort was the number of proposals that involve public, private collaboration in one form or another to improve innovation. For example, some of the proposals involved multi-stakeholder collaborations for developing new tools like biomarkers and new methodologies to support research. Also, the proposals include emphasizing the patient voice during the clinical development and review process around outcomes, around risk benefit assessments and the like.

Again, these are proposals that in many cases are based on promising efforts and initiatives that are under way now, but that could be accelerated. Chairman Upton from the Energy and Commerce Committee, emphasized that these proposals are far from final, but are intended to be the basis for further discussion and refinement, and those that can get bipartisan support from the committee and can get to a level of specificity and practicality for implementation will move forward in legislation.

So, not surprisingly, there have been a lot of comments and further discussions, and that's expected to lead to an updated set of proposals that will be released in the coming days. On the Senate side, the Health, Education, Labor and Pensions Committee has announced a process with workgroups to examine a spectrum

of medical product development and use issues to identify where new policy efforts could be beneficial.

It is under the leadership of Chairman Alexander, Ranking Member Murray, the Help Committee has established these bipartisan workgroups and outlined a plan to introduce their own legislative proposals based on this process later on in 2015. And President Obama in his budget announcement, has also described some targeted proposals for improving drug development.

This includes additional funding for antimicrobial research and a precision medicine initiative that supports -- that will involve support for a large cohort study to gather and analyze genetic and health data from perhaps a million Americans, as well as efforts to identify genetic markers across different types of disease areas, like in cancers.

I want to emphasize that not only do these potential federal policy initiatives reflect ideas from government, but also, from ideas outside of government. So, improvements in post market data collection, efforts on drugs and biologics today is leading to an enhanced potential for public health surveillance and research and improved innovation through the Sentinel initiative at FDA, as an example.

This is an effort that's supported by the FDA, but conducted through a privately led collaboration involving health plans, healthcare organizations and academic experts in industry. Efforts are also underway to begin active post market surveillance of medical devices enabled by the implementation of unique device identifiers, but once again, through a collaboration between FDA and a range of organizations like health plans and healthcare providers, hospitals and others that can develop and maintain longitudinal data for tracking safety. It's another example of public/private collaboration to address some of the important gaps in biomedical innovation evidence.

So, these are examples of how collaborative efforts are underway;

examples of how agencies in the federal government are working with the private sector to solve some innovation challenges.

Now, our first panel is involved in a number of these efforts; both efforts underway in the federal government and efforts underway through the private sector and public/private collaborations to address challenges in biomedical innovation. And I think they're all here with us this morning, so I'd like to invite our first panel up onto the stage right now, while I introduce them. And we're going to talk with them about some of these opportunities and some of what they see as the most important issues and developments in the biomedical innovation environment taking place right now.

So, throughout this discussion, we're going to hear a range of views and perspectives. We had originally, if you look at your agenda before getting here, you saw that we had four panelists on the list. Unfortunately, despite all of the progress that has occurred in biomedical innovation, that hasn't yet extended to acute upper respiratory infections, so -- in some ways, so Dr. Pamela McInnes couldn't be with us today. She is under the weather. We hope she'll get well quickly.

Now, we're very pleased to have with us today, Dr. Jeff Allen, the Executive Director of Friends of Cancer Research, Dr. Pamela Tenaerts, the Executive Director of the Clinical Trials Transformation Initiative and Dr. William Chin, Bill Chin, the Executive Vice President for Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America.

So, I am going to come over there and join you for this discussion, but while I get mic'd up, let me go ahead and pose the first topic that we'd like to talk about this morning, and that's the clinical trial process. So, this has been in the news a lot lately, both the importance of developing better evidence through clinical trials, as well as some of the challenges and costs of conduct of clinical trials and some of the difficulty of enrolling patients and collecting relevant data.

I think the upshot of all of that is that there is a lot of agreement that

there are many opportunities to make the clinical trial process more efficient, but some challenges in getting there. On the other hand, I know many of you all have been involved in steps to try to improve; the collection of data, the enrollment of patients, the conduct, the efficiency, the impact and the relevance of clinical trials.

So, I'd like to start off this topic with Pam, if you don't mind. Maybe you could give us a little bit of framing about some of the challenges and opportunities around the development and the conduct of clinical trials.

MS. TENAERTS: Well, thank you, Mark, and thank you for allowing us to be here today. It's exciting. It's an exciting time in biomedical innovation, and it's specifically exciting for us. We've been working on clinical trials for 20 years, and all of the sudden, it's hip. So it's kind of cool that people are actually thinking about it and trying to really make clinical trials better.

Some of the things that have come up, as you mentioned, are IRB issues, the use of a central IRB, and how some of the processes in clinical trials could potentially be improved to make things go faster, because the faster a clinical trial goes, the faster we'd have the evidence, one way or another, and the faster it could get to patients, which is ultimately what we want.

And what we looked at with the Clinical Trials Transformation Initiative is, why a single IRB of record was not used more often. Because at the time, there had been indications that FDA and OHRP were in favor of this, and this is now a couple of years ago. This more like four years ago, when we started this. This is before all of the recent discussions that started.

And what we did is, we interviewed IRB administrators and institutional officials to ask them why is this not happening; why are you not allowing -- when a sponsor comes to with the opportunity for a single IRB of record, why are you not allowing to have that happen? And what we found out through these interviews is that IRB administrators and institutional officials were confounding and combining into the

local IRB review, institutional responsibilities as well as IRB responsibilities.

So, when a sponsor would then come and say, hey, we've got this single IRB of record and everything will go faster, they did not want to give that up to that single IRB, because they weren't sure how to deal with the institutional responsibilities anymore. So, we created a document that specifically lined out what is an institution's responsibility, what is an IRB's responsibility and what could be handled by both, so that when a next request comes, an institution could look at that and take care of their institutional responsibilities, but allow the single IRB of record to take care of those responsibilities.

So, those recommendations came out. It included that you should use the considerations document to figure out how to parse things out, and that sponsors, when it's possible, that they should allow the -- require the use of a single IRB of record, because what we found, too, is that once an institution had used it, they were much more likely to use it again.

So then, we did a lot of presentations about this, and people would come up to us, and we launched a follow on project, because we said we still need more tools, because if you use a single IRB of record, you need an IRB authorization agreement between your institution and that IRB. And what might that look like?

And so, we are about to come out in the next couple of weeks with recommendations and a template for an IRB authorization agreement, along with a couple more -- I don't want to call them checklists, because people stop thinking when there is a checklist, but a couple more documents that allow an institution to look at their -- if they're ready to adopt a single IRB of record, have sponsors give them some framework around how do you pick a single IRB of record -- like who do you pick, because it doesn't have to be a commercial IRB. It could be an academic IRB or another IRB.

And then, for an IRB, a document to think about how they look at the

institution that they would be covering now. So, I think coming up with recommendations is not always enough. You need to give people the tools to create the change. And so, some of these things are possible and can happen, but tools have to be created so that people can get there.

Another thing that we found is, while some of this can potentially be legislated, a lot of stuff has been brought on by the clinical trial enterprise themselves. I mean, we've created a bunch of these problems ourselves. Typically, as an industry, when there was something that happened, we reacted with more forms, more things to be done, so that now, clinical trials have become so complex. I mean, I'm sure you've heard about this -- you know, they're calling it like $2.6 billion to create a treatment, and a lot of that is because of the complexity in clinical trials.

People start thinking about doing a clinical trial, and they add things on, because they might be talking to a physician investigator who is interested in something particular, so while we're there, why don't we ask that, too? And we'll ask that, too. And studies have found that 20 percent of procedures in clinical trials do not tie back to an endpoint. I mean, that's an internal problem of our industry. We need to think about that and not do things in a clinical trial that don't add to anything, that are never used in the evidence later.

And so, our Quality by Design project is looking at how we can build quality in from the beginning, so that we don't have -- and how do we think smartly about clinical trials? And just think, frankly, like think about it is you're trying to do, and don't just do the things you've done in the past because they've worked. So those are --

MR. MCCLELLAN: Those are --

MS. TENAERTS: -- some of my comments.

MR. MCCLELLAN: -- they sound like some very important initiatives. Let me just take a step back, Pam, so I can follow up a little bit about the IRB discussion. And IRBs do play a critical role in clinical trials and overseeing the conduct

of the trial and ethical conduct, in particular.

But you talked about some of the obstacles to moving towards a more centralized IRB approach. Let me just take a step back and think about why centralized IRBs might have advantages, especially for the larger multi-center trials that are becoming more common today.

MS. TENAERTS: So, a central IRB would have an advantage, because before you can start a trial, you have to have IRB approval -- Institutional Review approval at all of the institutions, which then takes care of looking -- making sure that the patient's safety and integrity of the trial is taken care of.

Typically now, if you have a trial with 20 sites, each of these sites has their own IRB. And as you can imagine, some of them meet monthly, some of them meet every two months. So, the timeline of getting all of these individual IRBs online and going takes a long time.

So, some institutions may have IRB approval in a month. Others, it may take three months, because the IRB has questions. It goes back and forth. And a study cannot start until an IRB review has taken place. In our Site Metric study, we found that sites that actually use a single IRB of record, a central IRB, the IRB approval was more streamlined. It happened faster for those sites, and they actually enrolled their patients faster. So, all of these steps have to be taken before a patient can be enrolled. And if we can streamline that process through a central IRB, that obviously streamlines the whole process down the road.

MR. MCCLELLAN: So, in this discussion about quality by design in the clinical trial process that CDTI has undertaken, and these examples around making the IRB process work more efficiently and effectively, you are trying to get at some of these cost barriers and avoidable costs and time delays in clinical trials.

Bill, can I turn to you, in terms of maybe giving us a little bit more context on what you see from a research and development industry perspective as some of the

challenges related to clinical trial implementation, and just how important these kinds of initiatives are?

MR. CHIN: Yeah, thanks, Mark. Well first of all, thanks for inviting me and us. I think this is a very important discussion. We all are dedicated to understanding how we can make better medicines more efficiently and effectively.

I think we're all here to try to advance, to at least endorse policies that advance about pharmaceutical science innovation, but also, to improve our regulatory decision making approaches. Clinical trials, as Pam has already indicated, is a key step, obviously, in determining whether potential new medicines are both effective and safe. And it's well known that the majority of the total cost in this system is embedded in this process.

I think people have estimated up to 2/3 of the cost. So, it is essential that we look harder and harder at the key impediments, hurdles, et cetera, that lead to a less efficient approach to clinical trials. Pam has talked about reliance IRBs, centralized IRBs. That's very important. I'd like to highlight maybe one or two areas.

So, a critical part of clinical trials is patient engagement and recruitment. And that is patient involvement in clinical trials. This is more of a challenge than you might imagine. In the United States, there is more and more problems in making patients aware of clinical trials, educating folks, but also, engaging them and recruiting to trials.

It's particularly difficult among underrepresented minorities, so that it's significant that Africa Americans or Hispanic Americans are greatly underrepresented in trials. Why is this? In part, it's because of awareness and historical issues. But we have to do much better in this.

Pharma, working with the National Minority Equality Forum, really has worked over the last year to begin a process of awareness called I'm In. This provides more awareness for clinical trials, the importance thereof, and the importance of

engagement really, for family and loved ones. So, that's one part of it.

The other is, once you have raised awareness, how do you actually recruit patients, really encourage patients to participate? And I think there are a number of groups trying to do that, as well. So, that's one feature. And this is just only -- we're only mentioning a few. Right, Pam (Laughter)?

MS. TENAERTS: We could talk for hours.

MR. CHIN: Right. We could talk for hours on this.

But the second one, you know, comes from my own background. I am a physician scientist, a faculty member at Harvard Medical School, where we spent a lot of time trying to understand how we can better train clinical scientists to be the ones who actually perform some of these studies.

You may or may not know, there's a dearth of such individuals in this country and around the world. How can we actually be capable of you know, divining better clinical trial designs, thinking about all of the problems and trying to solve them without that? And I think that's another issue, Mark, that we need to face from a policy perspective, is training, not only physicians, but also other scientists who are very interested in clinical medicine and clinical trials in order to make this happen.

MR. MCCLELLAN: Do you see any steps taking place now that are helping with that issue? I mean, you mentioned some of the initiatives related to education, outreach, encouragement of participation for underrepresented minorities in clinical trials. I'm wondering if there are similar efforts underway that you see as promising on the -- in the process of getting more expertise in the conducting of the trials.

MR. CHIN: Well, this is an ongoing challenge. You have young physicians and scientists wondering what kind of career do you have in this area. Physicians, particularly, have tremendous challenges in terms of their usual debt when they get to this point, and really, having almost a seduction to go into practice rather

than to go into this very, very important field.

There are important steps, though, that have been made. I think the NIH with the Clinical Translational Science Award, CTSAs, have sought to provide more funding to allow prospective clinical scientists to actually appreciate what this is all about; to actually have education in this. And I think we're slowly seeing some progress in this.

I know that at Harvard, there's a lot of activity -- Duke, and many other places. So, I think this is hopeful, but I'm just worried that it may not be enough.

MR. MCCLELLAN: Yeah. I mean, a lot of the patients who I assume you'd like to get into trials, are not necessarily going to Harvard or Duke or some of these major centers, but are out in the community. And that seems to be an especially important issue, as trials aim to get more targeted around particular types of patients with genetic profiles or other characteristics that fit in with the pressure towards --

MR. CHIN: A great, great point.

MR. MCCLELLAN: -- personal medicine.

MR. CHIN: Because while I'll focus on patient awareness and engagement, and we talked about the physicians who do the trial, a critical, critical part about this system are the healthcare providers. They also need to be part of discussions and the decisions here. And I fear, we all fear that perhaps, we're missing that part; that again, we talk about busy physicians who may not want to be clinical scientists.

What about those physicians who have to take care of patients, and they spend endless hours doing that, and then now, we're asking them to talk to patients about engaging in clinical trials. Many of them are not aware and many of them don't have the time. How do we help physicians who -- and healthcare professionals help us in this process, as well?

MR. MCCLELLAN: Jeff, I'm going to turn to you on this same topic. This

is -- the cancer research is an area where there is a tremendous amount of activity going on now both in terms of the range of therapies, not only traditional drugs or even more traditional biologics, immune therapies, other combination approaches, how they're being developed. Increasing evidence that a patient's genetic profile really does matter; it's not just the type of cancer you get, but the metabolic profile and the pathways that are disrupted by the cancer.

All of this suggests that having more and more targeted trials for cancer therapies would be really helpful. But as Janet Woodcock from FDA likes to point out, only a very small fraction of adults with cancer actually get into some kind of clinical trials. I know this has been an important issue for Friends of Cancer Research. How are we doing? Are we making progress?

MR. ALLEN: Progress is slower than I think everyone in this room would like, but I think we're making progress in terms of looking at new approaches to address this problem. And specifically, what's happening in the field of oncology, at least in many -- in several different tumor types, is that as the underlying biology of the disease becomes better understood, as you said, it becomes evident that different targeted approaches to go after genetic alterations that are driving the cancerous growth, can be positive interventions.

But the challenge is, that as you parse out these different genetic components, the populations that you test them in become smaller and smaller, and this puts additional stress on the system that has already been described here, both in terms of finding the patients, making sure that the trials are widely enough available, because the patients are going to be spread much further in between. You may only have a couple of patients at any given institution that have a particular genetic alteration of interest for the drug that you're trying to test.

So, the system really needs to be flipped around. And this is what we're trying to work on in the concept in lung cancer, with regards to the lung cancer master

protocol that was launched less than a year ago, And to kind of capitalize on some of the concepts that have already been raised, this was one of the first trials that utilized a centralized IRB that's being set up by the National Cancer Institute.

And proof in concept here, to Pam's point is what we were able to see in the Lung-MAP study, which many of the institutions did utilize the NCI's centralized IRB, and they were able to get up and running much faster. Within a couple of months of the study, several hundred sites are open. It's now available in 42 states in well over 400 different sites that are available to offer this trial to patients.

You know, that doesn't alleviate all of the burdens here, but it speaks to the need for you know, what is possible in terms of ramping up a trial. And to Bill's points of you know, making sure that we had a system that more physicians can be involved in, to date, over half of the patients that have been enrolled in Lung-MAP have been done through a community based setting rather than major academic institutions.

So, part of the problem here is availability. You know, I think that that's only one component, you know, of making sure that we're able to address these challenges, but I think some of the unique properties of the Lung-MAP study is that it's bringing innovative new technologies where they may not otherwise be accessible.

So, the concept of having genetic screening available at all of these different sites is relatively new, and I hope that drives participation in the trial, because perhaps, for some of the first times, some of these smaller facilities are able to utilize the biopsies they might be giving to lung cancer patients already. And there's a system in place now that they can get full genome sequencing through our partner in foundation medicine to be able to shuttle the patients to the most appropriate arm of the trial.

And what this does is combine testing for multiple different drugs within the same protocol, and this is meant to evolve over time. So, not only do you have the platform in place that you're screening patients to make sure they're getting the treatment that's best fit for them, the protocol is constructing in a way that new drugs

can essentially plug in and plug out over time.

So, we're not going through this multi-year process of setting up a new protocol every time you find an interesting new drug to research. It essentially can just be folded into the protocol, and so long as the screening is continuing in providing patients and physicians the information about the genetic makeup of the tumors, then essentially, the trial just keeps building and rolling along as the new drugs and biomarker pairs become available.

MR. MCCLELLAN: So, this is kind of the opposite of the one-off trial approach where everybody gets together and builds an infrastructure to address one important question. This is really about a whole area of cancer therapy. And maybe you can say a little bit more about the patient population that's involved in this effort.

MR. ALLEN: Right. So, it is in squamous cell lung cancer, which is unfortunately, one of the most deadly forms of lung cancer that to date, hasn't necessarily had the same progress made in terms of biologically targeted agents as some other forms of lung cancer or melanoma or other diseases, but based on the Cancer Genome Atlas, it has become evident that many of these alterations that could be driving the cancer are present in squamous cell carcinoma of the lung.

So, in terms of identifying the patients that could be involved here, it's really based on that initial genetic screen, where there are several targeted arms in which a patient that is positive for one of these biomarker pairs is then shuttled into that arm. A unique feature of the lung map, also, is the availability of a non-match arm.

So, if a patient is screened for the trial and doesn't match one of the currently available biomarker arms, there is one of these immuno therapies that you mentioned that is being tested in the context of this study. So, there is an experimental drug essentially for everyone, which historically, has been a concern in some clinical trials that patients may feel like they're enrolling in a clinical trial for access to the experimental agent.

But you know, in many cases, for the integrity of understanding what the contribution of that experimental agent is, you know, randomization is necessary to occur. Now in oncology, what this means is availability of standard of care versus the experimental arm, so it's not necessarily the historic concerns of placebo, so to speak.

But the goal here is to rapidly test some of these targeted new agents in a way that wouldn't be able to be done without this type of construct. You know, going back to the idea of having to find the patients -- you know, some of the alterations that are being tested for in Lung-MAP are very rare. You know, when it's 5 percent of this population of lung cancer patients, even finding them would be very difficult, and frankly, increase the cost and time constraints on the trial, because the screen failure rate, so to speak, you'd be -- you know, 95 out of a hundred patients might not be fit for the trial.

But screening so many up front, you're able to capitalize on that information and not lose it. So, the time component of Lung-MAP as well as the cost are really a huge advancement here. You know, it's estimated that the per patient cost for Lung-MAP is well over half of what it would be to conduct this study or a traditional phase III study. So, it's a huge positive, both from the efficiencies of starting the trial, getting the drugs in, getting the data you need to get them onto the market, but simply from an affordability standpoint in an environment where conducting these trials continues to rise.

SPEAKER: I think that a lung map, really along with other studies similar to that, like I-SPY, I-SPY 2, really illustrates what we think we can do.

MR. MCCLELLAN: I-SPY, a set of studies for breast cancer to allow ongoing multi-center enrollment in evolving treatment arms is (Inaudible).

SPEAKER: So in a sense, again, adaptive designs that in a sort of -- if you look back a couple of decades ago, would not even have been considered, because the idea was you had to have randomized controlled studies with blinding, et cetera. And I think these experiments and pilots in a sense, I think, illustrate for us the

possibility of streamlining, changing study design to still get you answers quickly.

We need to be challenged to continue to do this. And I think the other thing that's really wonderful about the work that Jeff and his colleagues have done is it's been done in collaboration with --

MS. TENAERTS: I was just going to say that.

SPEAKER: -- with the FDA, with companies and patient advocacy groups.

(Simultaneous discussion)

SPEAKER: And a large number of academic centers.

SPEAKER: Absolutely.

SPEAKER: Oncology groups.

MS. TENAERTS: And that has really been sort of the newer trend in the last couple of years, I think, where people are seeing that if you work together, multi stakeholder, everybody at the table as an equal partner, that you really do come up with better solutions, and that it helps the field.

And sort of this isolation is going away a little bit. And hopefully, with some of these new initiatives, it's even going away further.

MR. MCCLELLAN: This all sounds good, you know, clearly transforming the way clinical trials are being done in areas like breast cancer and squamous cell lung cancer through things like centralized IRBs that are well developed and consistently applied at all of the sites, steps that make it easier for community based providers to participate, a broader range of treatment arms which makes patients feel like they're getting plugged into a good system, steps to make more consistent and effective data collection take place.

All of that sounds good, but I have to say, from what I've seen of these efforts, they don't happen easily. So, Laura Esserman with the I-SPY effort has kind of devoted her life to getting this together. Ellen Siegel, who has more energy than -- as

Jeff knows (Laughter) better than anyone, has more energy on trying to promote effective research than just about anyone I know, was spending most of that past year plus to help get this off the ground.

There is a lot of willingness there, but these collaborations don't seem to happen quickly or easily. From what we've seen so far in these areas, what would it take to make this is a more standard and replicable process for progress in clinical trials in a broader range of areas? Or is there just continue to be just a lot of hard work on disease area by disease area?

SPEAKER: You know, I'd like to think that no doubt that projects like these could not have got up and running without the leadership of people like Ellen Siegel or Laura Esserman. And hopefully, that was required so much in these two instances because they were both so new within the field.

There has been, I think, following you know, the lead of projects like I-SPY or Lung-MAP and increased interest in developing these types of clinical trial networks. It doesn't mean that it inherently becomes easy, but at least there is a little bit of a model to follow. And you know, from our experience, we certainly tried to learn as much as we could, as those in I-SPY or the battle lung cancer trial with similar approach had learned.

We had some differences in Lung-MAP that still presented some new challenges, you know, notably being that the design of Lung-MAP is one to be of registration quality, so that the drugs that succeed through this are fit for a regulatory decision at the end of the day, rather than just an exploratory type study.

But I hope there are a lot of lessons learning. You know, we certainly have talked to a lot of people in other disease sites that are working to replicate them. You know, it's not a walk in the park, but I think, you know, as we get better at this and we understand how to collaborate better and understand what each organization and entity needs to put into these successful partnerships, hopefully, they'll be able to

become more routine and get up and running even faster than they have to date.

SPEAKER: Basically, it's getting over it can't be done philosophy. And before these efforts, the wisdom at the time was, it can't be done. And so, having efforts like this move along and show progress suggest that well, it can be done in some areas. So, let's all challenge ourselves to think how it may be useful in other areas.

MS. TENAERTS: But the important part is, too, as Jeff alluded to, is that people have to then also be transparent about how this came about, how this worked, what the problems were so that you can actually learn from them, because to just go ahead and do them and then never say a word about it, doesn't help anybody. Right?

It all has to be in the public domain so other people can learn. And you guys have done a fantastic job of that -- speaking everywhere and letting people know about what the issues were, how you've overcome them, what you didn't overcome, so that other people can learn from it.

MR. MCCLELLAN: So, making sure we capture the key elements --

MS. TENAERTS: Yes, yes.

MR. MCCLELLAN: -- of this process and get that out there. That seems like one important takeaway lesson for accelerating progress.

Now, let me go back to some of my introductory comments about whether you all see any policy implications here, either in terms of legislative activities that groups like the Energy and Commerce and the Health, Education, Labor and Pension Committee should be considering. I know there's some focusing on some efforts related to clinical trial improvement, or in terms of the other big issue, which is appropriation.

So, I know more money is better, but are there any implications here for how, say, NIH funding to support clinical research or how company funding to support clinical research should be directed?

SPEAKER: Well, clearly, we need to do much more work in many of

these areas. I mean, people always are asking me, why isn't it easier to make medicines. We have all of the technologies. We have many of the tools that weren't existent maybe even 10 years ago. How come it's still such a tedious and expensive process?

And I think in large part, it is still -- the answer still is that disease is complex. We still don't understand what causes most diseases. Cancer is actually becoming more of an exception, amazingly, because of the great investment in the building of our knowledge in cancer over 40, 50 years. We also don't understand what causes the heterogeneity of disease. What makes two individuals with the same disease manifest the disease differently? How they respond to therapy, et cetera, and how they develop complications.

So, the point here is that we need more knowledge. We need more knowledge on the basic level. So, that is NIH and groups like that. And certainly, there is great interest in increasing the funding there. There is, however, we feel, an important thing to remember is that it's not just about basic science.

In order to make better medicines, we need to translate those ideas into reality, which is a form of a molecule or (Inaudible), et cetera. And that takes other groups like industry. I would argue very much that patient advocacy groups have to play a key role; academics will play a key role. How do you bring all of this together and sort of not sort of fund one versus the other?

So, we're in a difficult situation where of course, NIH needs more funding. But if it's funding from other groups, then we feel that that would be missing the boat. You're taking funds from one pocket and sort of it putting it in the other, and that won't help the whole system.

MS. TENAERTS: So, I mean, I basically also agree that a lot of our basic science and people looking at science to evaluate it probably need more money. Where I disagree is, I'm not sure that bringing more money to the specific clinical trial

piece of it is what we need, because as Jeff said, the Lung-MAP study is actually eventually going to be a cheaper study for patients.

So, it doesn't always have to be more money. It's just thinking better about how we do some of the things. And in clinical trials, I think sometimes it might better to say instead of a hundred million, what if you had 50 million, what would you do? And you probably would get to a much more targeted outcome, rather than more money (Laughs).

MR. MCCLELLAN: Sounds like a good metric to track in terms of the efficiency trial. You know, what do you get in terms of enrollment, study completion around meaningful endpoints for the dollars that are being spent.

MS. TENAERTS: Right, right.

MR. MCCLELLAN: And I'm not sure that's something that we really track a lot. Jeff, what do you think? Most important for Congress and appropriators to be focusing on.

MR. ALLEN: You know, the funding aspect, I don't think can be understated. And I think one of the challenges with the annual budget cycle is that it's -- from a scientific perspective, while science itself moves fast, the process of start to beginning still seems kind of slow.

MS. TENAERTS: Yes.

MR. ALLEN: But I think, you know, where projects like Lung-MAP can demonstrate what that process actually is, is pretty remarkable. You know, when you look at projects that are very early on, basic research things like the Cancer Genome Atlas, that when the NCI spearheaded that initiative several years ago, I'm confident they got a lot of pushback. You know, what is going to come from all of this data? Are we really going to get anything useable out of it?

And this is probably just scratching the surface as to what could come out of that data. But what the study team that has been leading Lung-MAP was able to

do is start to discern molecular targets in this type of cancer that drugs can be developed toward. You know?

The hypothesis was based on some of those results from the Cancer Genome Atlas -- very rapidly developing the drugs, matching them to the most promising targets, getting them in a study that is designed to be more efficient than just slowly walking your way toward data, but to really kind of jump in with two feet here and say, we have some early evidence. How do we design a study that's more efficient, that is, in many ways, for successful compounds, combining the different phases of development?

So, we're getting to that point of regulatory decision much faster than the standard approach that has been applied thus far. And that's really been done out of careful design from the experts from the academic institutions, the National Cancer Institute, who has you know, largely spearheaded this project, the FDA, who has been a huge, willing partner to put their scientific expertise at the outset of this to help define how does the study need to be conducted so that the data that comes out of it is most useable for our intents and purposes.

And you know, it's taken everyone involved -- you know, the companies, the academics, the advocates, the government, to start thinking about ways that they could do things differently, and oftentimes, it's had to kind of push the envelope and bend things a little bit. You know?

In order to put this study on a new trajectory, even industry, who operates from a business standpoint of doing things as efficiently as possible, you know, they had to think about ways to do things differently and do things even faster. And maybe that made people uncomfortable. That's why we have people like Ellen Siegel to be able to drive these things forward. But at the end of the day, everyone was able to look at where they could make the steps that involved their individual organizations more efficient and faster, and the net gain has been huge.

MR. MCCLELLAN: There's a great discussion around clinical trials, where we are, some of the challenges and where we're headed. Actually, it gives me some sense of real promise for the future, even though we're not all the way there yet. Despite all of this progress and potential future progress around better evidence from clinical trials, one of the biggest themes in recent years has been so-called real world evidence, which seems like -- and it's going to be a little bit hard for me to understand exactly what it is, but it seems like what it's not is evidence developed in well designed, carefully controlled clinical trials, but evidence that's coming from elsewhere.

And we hear about this a lot, so despite all of this progress from clinical trials, Bill, I know you view this as an important area for further development for biomedical innovation, as well. Can you say a little bit about why?

MR. CHIN: Sure, Mark. You protest that you don't know that much about real world evidence --

MR. MCCLELLAN: (Laughter) Well, I was going to define it --

(Simultaneous discussion)

MR. CHIN: -- but you talked about your efforts in Sentinel and (Inaudible).

MR. MCCLELLAN: It's hard to define it, exactly.

MR. CHIN: Clearly, we have had a lot of experience using so-called unstructured or real world evidence in helping us look at our medicines in terms of certainly safety from the Sentinel perspective, the post market surveillance aspect of it.

Our question really is, what is the future role of such information? So, I'm referring to information that's embedded in, for instance, electronic medical records, just as an example. How could we eventually develop the tools and the methods to utilize this information to complement regulatory decision making? So, that's just one question.

Now, we realize that it might be early to ask that it replace it, for sure, but

what we think is that it's necessary to take the steps to understand where it might play a role. And so, it's very important to caution. It's not a cure-all, so we're not saying that we're going to use this information to complement everything, but there may be specific diseases, conditions, patient subsets where this kind of information could be particularly useful.

We like to say, after all, you know, once the medicines are in the patient population, what we do is we gather real world evidence. That information is not in the form of now randomized controlled studies anymore, and yet, we have to make decisions about how useful those medicines are, continue to be, how safe they continue to be.

So, real world evidence for us is just simply an area that we would urge all of us to be thinking about and exploring. It's here. All the data are here. Some would say there's too much data, but it also means that we should be actually encouraged to utilize studies, pilots in order to learn the tools and the methods to be able to do this.

Now, we know that real world evidence has biases. We appreciate that. But how, despite that, can they be utilized?

MR. MCCLELLAN: So I mean, the real world evidence does seem to be getting additional attention and use. And Bill, you noted the regulatory uses and FDA has expanded its Sentinel initiative activities and is now conducting studies on a regular basis that not only can help address issues that arise in the post market setting, but that also can be part of the life cycle evaluation of a product where there are questions that may come up in pre-market development that it's not feasible to address there because of sample size issues or questions about real world use.

Having an infrastructure in place to develop that evidence can help. Now, most of those regulatory uses seem to me to have been about safety questions, where these observational data, non-randomized data are probably easiest to use when

you're looking for something that just shouldn't happen or just shouldn't happen very often; very rare events that are occurring more commonly, and things like that. So, that makes it a good fit potentially for some safety questions.

On the other hand, there has been a lot of interest -- maybe not so much yet on the regulatory side, but certainly on the reimbursement side from payers in really wanting to understand in the real world, what kind of impact different clinical alternatives have in populations that may not have been exactly the same as those tested. You know, we talked about minority populations not being well represented, elderly populations, and so forth, not having -- the payers feeling that they don't have quite the kind of evidence that they'd like on particular uses and settings where you know, things go wrong.

Adherence might be an issue where the treatment options maybe are more complicated with newer alternatives or suggestive evidence being developed that other treatments may be better or less costly. I haven't seen as much definitive work on, I guess what you might call the effectiveness or comparative effectiveness side using real world evidence yet, though this is obviously a high priority for Pecori, for many of the payers, and I think increasingly, for the manufacturer, as well.

So, there is a question in here, which is maybe -- I don't know, Bill, if you want to take this one, or Jeff or others, but where do you see this kind of evidence headed? I mean, it is a lot of potential there, but it seems like we're still a way from really understanding how to use the -- how to develop and use these kinds of data effectively.

MS. TENAERTS: So, with CTTI, we're actually conducting a project in which we are looking at the Sentinel data set to see if we can use that set to identify patients for clinical trials, and then eventually, to maybe see if you could use that set to sort of do a passive clinical trial to see what then happens to those trials.

And we did a one year evaluation of what the issues could be and

created a report, and just this year, we've taken two use cases within inclusion exclusion criteria and translated those into specifications that could be run through Sentinel to see if patients could be identified. I mean, there are some issues with that, of course, because if a company changes their healthcare plan; a patient goes from one plan to the next, it's not exactly clear if you can link those two and things of that nature.

But we have taken steps to see if there is a methodology that could be -- where you could repurpose the mini Sentinel safety system to sort of create clinical trials and see if that's possible. So, we're definitely working on that. It's a work in progress and it's hard, but yeah.

SPEAKER: Well you know, one limitation thus far has probably been the availability of some of these large data sets, and it requires them to be even more complex when you're looking at potential effectors of efficacy, so to speak.

MS. TENAERTS: Yes.

MR. ALLEN: But perhaps, this will move forward with the administration's proposal on you know, collecting the genomes on a million Americans. You know, I don't think it will reach the point of establishing clear causal effects between some of these factors, but having a database that is deep enough to collect genetic information could be a hypothesis generating tool to then conduct different studies of responders and non-responders, and start to try and parse out what factors might contribute to that, better than what has been done in the post market setting in the past.

I think it's very complex, so you know, you can't overestimate the importance of these datasets or the challenges associated with reaching a conclusion, but without it, we're kind of left in the status quo, which is sort of a bit of guesswork.

At least in oncology, you know, while we've painted a bit of a promising picture here in terms of new drugs that are having great effects, but very rarely are they across the board in 100 percent of patients that take them, see the response. So, there's still a lot that needs to be understood about associated factors that could be

responsible for a response or a lack of response for many new treatments.

MR. CHIN: Mark, I agree with both Pam and Jeff, that these are still early days. I think we look towards the experience of Sentinel, mini Sentinel as a lead to potential success in trying to understand events, in this case safety, you know, after approval.

I don't think it's a real stretch of the imagination to think that we could be able or we should be able to capture information on benefit -- on efficacy. We have to define it well. And of course, depending on the disease, that varies. I think the question for us is, there is a wealth of -- and there will continue to be a wealth of data, let's say post approval, post market. Are we going to just ignore all of that information from an efficacy perspective, or will we be able to figure out how to use them in a good way?

Just try to understand there will be biases. How do you sort of overcome those? And then, allow that information to help complement, supplement the information that we get in the preapproval process. I think I like to sort of quote Janet Woodcock when she says that when you gather all of this information at the FDA and decide on whether a drug has sufficient benefit risk, it is in many ways, still a prediction; a prediction that this will more than likely be beneficial outweighing risks. So, it's a prediction.

So, how do you make that prediction become more real in time? You could mandate more studies, but we know that that's impractical. But if the data are there and we learn how to use those data, then perhaps they could help us.

MS. TENAERTS: And I think it's going to become even more important, because currently, there is more and more devices and drugs being approved under accelerated pathways. So really, you're even moving the lever forward a little bit with potentially, you know, even less evidence in many ways, so that the post marketing approval situation is going to have to be better understood.

And I think not only is it Sentinel initiatives or things like that, but

registries. There's a lot of registries being created by patient advocacy groups, by professional organizations. And to leverage that in terms of getting evidence out of there, I think will be really important, and we really need to understand how to do that better.

MR. MCCLELLAN: There are lots of opportunities for more data turning into potentially more real world evidence. Those are some challenges that you've described in getting from the data to the evidence.

I'd like to turn to another big theme that we've seen recently, and that I know all of you have played a part in, and that's the increasing importance of patient perspectives and patient experience in all of this evidence development process, whether it's clinical trials or real world evidence.

Just to stick with the real world evidence side, a lot of the work that Sentinel's done so far that's already been discussed and a lot of the potential, Bill, Jeff and Pam that you're alluding to involves using things like insurance claims data on utilization, electronic medical record data on the clinical status of patients.

But if you know, we look around us today in 2015, really, the most notable shift in the information and evidence that people are developing and using in their real lives is information coming from people themselves. Their own -- in this case, it would be their own clinical experiences, their quality of life, as Bill was saying earlier, how the benefit risk prediction really amounts to a reality, and for an individual patient, it's not a prediction. It's a reality. It's one or the other. And the clinical outcome measures may correlate well with what matters to the patient, but they certainly don't always capture it.

So, I'd like to talk a little bit about where you all see the role of patient experience and perspectives going forward in these issues related to clinical trials and real world evidence. Maybe one place to start on this is the data and endpoints that are collected. So, FDA has recently had some approvals and labeling changes based not

on what might be considered hard clinical endpoints by doctors, but on quality of life measures from patients.

But this is still only a small minority of the endpoints and clinical trials. I think only a limited number of trials conducted in the last few years for product registration have involved patient reported outcomes. Is that going to change, and should it, and how fast?

MR. ALLEN: I think it can change. You know, we've seen initiatives that demonstrate that this is not impossible to generate this data. You know? And people volunteer this data all the time through the use of now common web sites and things like Patients Like Me, where you can aggregate the experience of patients on a variety of different treatments, or even just with a variety of different diseases, to try and understand how diseases or interventions are impacting the daily lives of the people that are dealing with it.

You know, I think maybe the difference here is that a lot of attention on PROs is often placed on how it can contribute to the pre-market aspect of the product. And that adds to some of the complexity. You know, I think historically, endpoints that have been used, at least in oncology, are how a drug affects a disease. And it doesn't necessarily reflect how the drug affects the person, so to speak. And those are sometimes easier to measure.

It's comparatively easy to understand if a tumor is shrinking because of the results of taking a treatment. You know? But like you said, the instances where a primary endpoint being what a patient reports happening to them, the examples are pretty few and far between. And I think we do need to think about how patient reported outcomes or patient experiences can complement some of the traditional measures for drug efficacy in terms of the pre-market space.

But then, there's this whole post-market space that I think you know, there's a growing interest, and organizations that have a huge reach to different patient

constituencies that are interested in understanding what their constituents -- what's happening with the constituents by using different therapeutic interventions.

And there have been some great steps taken forward in terms of policy within the last FDA reauthorization. There was the establishment of a patient focused drug development program which provided the resources and set up the infrastructure for the FDA to conduct. They're in the midst of 20 different meetings; to solicit information directly from patients and patient advocates about the experience with diseases and potential interventions. And the goal is to help aggregate that information and add it to regulatory decision making.

I think moving forward, there could be opportunities of looking at providing guidance into methodologies that different organizations could employ when working with their constituents to make sure that the information that's brought back to researchers or to the FDA is scientifically rigorous enough to be able to be used for regulatory purposes.

And you know, I think most organizations that provide direct services to patients are there because they provide very important services. They're not necessarily set up to be research engines, but they have the data. So you know, it goes back to collaboration in terms of trying to align what the needs are for different stakeholders.

But certainly, organizations that are conducting -- giving services to patients and where there's interest to better understand how they can improve the lives of the patients that they represent -- you know, having the methodological guidance on how to generate this patient experience data better would go a long way to advancing the field.

MS. TENAERTS: I think there is actually -- Jeff is exactly right. There's a couple of things that people need to think of when they talk about patient engagement. I think first of all, the definition of what it is, is a big deal, and I think that there's a

collective side if people start talking about let's define what we mean.

But what we don't have -- we don't have the methodology to turn those patient stories quite yet into some sort of a science that can be objectively used. And I think creating that science would be fantastic. There are groups working on that. MDIC, the Medical Device Innovation Consortium, has a project on it and has done some really good work. And it would be good that we don't always reinvent the wheel, because we are very good at that, too.

We try to think always that we're very special. Every disease is special and you know, every group is special. But really, there's a lot of commonalities. So, just sort of think of that. But then the other piece is to sort of -- how to best engage with patient groups and how to best engage with patients. And there really aren't any best practices about that, either.

Like, what are the groups to engage with? How do you set that up in a way that's right, legally and ethically, and those kind of things? We're coming up with best practices for that, and they'll be out soon, but I think that's been something that's missing, too. It's not only the science of how to turn these stories into something you can use in the drug development space, but then, how to actually engage with the patient and what does that look like? How can you best do that?

MR. CHIN: So, I agree with Jeff and Pam, that there is a great need and desire to focus on patients. We're all here to meet the needs of patients. Unfortunately, it's easier said than done.

And so, we agree that in the area of patient focused drug discovery and development, there is the need to understand what the science of patient input is all about. I think we all believe that there is a science involved here, and that whether it's in social sciences or some other areas, how do you bring to bear what is beginning to be learned about patient desires, inputs, behavior, et cetera, and to be able to, as you say, Pam, you know, develop the tools and standards -- to be able to objectively put this

information in place, and to use it, post market, yeah, but pre-market, as you pointed out, Jeff, in terms of identifying new endpoints and new study designs, or later in the process of actually using this information for regulatory decision making.

I really do believe that this workshops that the FDA began a couple of years back have been terrific. You know, one example as a physician, occasionally, I've seen patients with sickle cell anemia, and I've thought all about you know, pain and a lot of features that are traditionally sort of looked at in these patients.

But one thing that came out in one of these workshops is to understand that fatigue is a tremendous factor. And it's somehow lost, or not fully captured. So, how can we together understand better what that science is all about? How do we apply it to the ways that I've talked about? And also, we may not have time to talk about this more, but link it with drug development tools such as bar markers.

We think of patient focused drug development as also PROs, Patient Reported Outcomes -- patient standard outcomes, because we believe it's not just about patient reporting, but what about family? What about healthcare providers? They also provide very important information. So, how can we put this all together to make the whole package of what our endpoints are really, in the end, meaningful to what counts the most, which are our patients?

MR. MCCLELLAN: So, did you have a comment?

MS. TENAERTS: Yeah, I just want to say that we believe that patients have a role in every step of drug development -- of development of treatments, not just drugs. It really also -- it's not only the endpoints and the outcomes, but the question. Ask a question that matters to everybody; not just to the companies, but to the patients.

And then, if you ask a question that matters and have inclusion criteria that are relevant and target the population at need and have endpoints that matter, and then hopefully, in the end, the treatment that makes something better, you won't have problems as much with enrollment of patients. Patients will want to be in your trials,

because it matters to them.

Now, sometimes, there are trials where patients go, oh, I'd rather be in this trial. This one doesn't interest me. It's not relevant. So, I think --

MR. MCCLELLAN: Pam, are you starting to see some best practices for --

MS. TENAERTS: Yes.

MR. MCCLELLAN: -- having active patients --

MS. TENAERTS: That's what we're working -- yes.

MR. MCCLELLAN: -- involvement -- not as involvement, I guess leadership and --

(Simultaneous discussion)

MS. TENAERTS: Yeah, equal partners in the drug development --

MR. MCCLELLAN: -- at every stage of this?

MS. TENAERTS: -- process.

MR. MCCLELLAN: Yeah.

MS. TENAERTS: Not just in the endpoints, not just in the traditional, oh, we come to you because we need help with enrollment. It's really the whole process, I think. And that may be the Sentinel change that we need to see, is to really make it worthwhile for the people that in the end, it's made for.

MR. MCCLELLAN: Very interesting. I would like to -- I'm going to turn to questions from the audience in a minute, but I just wanted to follow up on one theme that seems to be emerging across all of these areas, whether it's patient engagement and participation or new methods for designing and conducting clinical trials, or dealing with some of these thorny issues around methods for using real world evidence effectively and appropriately.

This stuff is hard (Laughter). And as you all have noted, there is a lot of activity going on. There has been past legislation that's urged FDA or directed or

mandated FDA to take more steps in this direction. Jeff, you mentioned, for example, around patient reported outcomes -- these steps to engage patient groups. FDA has also been directed and is taking a lot of effort on its own to be clear about benefit risk methods and frameworks in particular disease areas.

But this is hard work, and while FDA is really good at holding meetings, especially when Congress tells them to do so, and the staff, they're trying hard to keep up with everything that's going on in these fields, it's very limited resources for some very big problems. And I wonder if that's what's behind what seems like a big theme in many of the legislative proposals that are being discussed now in this whole area by medical innovation. And that's more public/private collaboration.

So, whether it's around patient reported outcomes or biomarker collaboration or methods for study design, you can find something in the help committee list or in some of the topics that the Energy and Commerce Committee has worked on that lay out some role for a kind of public/private collaboration around addressing these issues.

Now, this seems like an area where there's some progress going on; clearly, a lot of activity that you all have emphasized. But it's also an area that makes many people nervous, that you've got the FDA working too closely perhaps with industry, with patient groups that also work closely or get support from industry.

Are these best practices for doing this? You all have been involved in a lot of these collaborations. Are there some more general lessons going forward, since this does seem to be such a hallmark of many of the proposals that are being considered right now?

MR. CHIN: Well, some have specifically said that the reason why there's more interest in public/private partnerships is that we're out of solutions. And the only way to do this is to try to work together. And the truth of the matter is -- I think Pam, you've said it, is that many of the issue we face are indeed, complex. And the only way

to sort of really approach it is probably to be sure that you have multiple perspectives of the same problem and try to attack them.

I think no one sort of argued that these kinds of things are important and can be very useful. And we can provide some examples. There is something that continues to sort of limit what we do, and that's human nature. When you bring all of these groups together, there's always the different perspectives, but sort of a desire to own the process.

How do we sort of diffuse that? How do we align the goals of everybody in a partnership? I think that's also been challenging. When you bring in industry and you bring in other groups, there's always the challenge of, if there's a new idea, who owns it, et cetera? One example, if Pam McInnes were well and here, would probably talk about the accelerated medicines partnership.

And this is something that Francis Collins initiated with a number of groups -- industry, but also very importantly, patient advocacy groups to focus on a number of diseases. But they worked together to define to define new targets -- the starting points for new medicines. This had never been done before.

And I sit on the executive steering committee and watch the progress here. It's really phenomenal, what's happening. The fruit still is not for public consumption just yet, because there still needs to be more progress made. But it's impressive how these companies, working together with NIH and also academics and patient advocacy groups really, I think, will lead to something very useful. It's very much kin to what might happen in precision medicine and the like.

MS. TENAERTS: And I think public/private partnerships have a great role to play in this. What we need to think about though, is they take a while to launch and to sort of get into a groove. I don't know if that was the same.

MR. CHIN: Yeah.

MS. TENAERTS: People need to learn to trust each other. Trust is a big

thing in these public/private partnerships, because if you don't have the trust that people are there for the greater good -- it's kind of like who owns it. Really, nobody owns it. Everyone owns it. Right? Not one individual owns the solution, and that's really how it should be.

It's really for the public good that we're doing this, to try to make this better. And I think if you have trust, then you can have the hard discussions. There's always some questions sometimes about -- like is it ethical to have all these people in the room, so to speak. But if you have everyone in the room, then really, everyone -- it drowns out the -- sort of somebody having more say than another, so it kind of equalizes the playing field.

And I think having these discussions and having the trust where you can say the things that are really the barriers of changing something is the only way that you can create a solution around it. It's one of those Greenpeace slogans. Right? If you're not part of the solution, you're part of the problem, a little bit. So, that's really what in a public/private partnership you can address, because then, the problems can be put in the room, and it's the power of everyone thinking and everybody bringing their perspective that will get us solutions, is what I think.

MR. ALLEN: And I think the important thing to stress about the emphasis on public/private partnerships is that it's bringing together critical expertise.

MS. TENAERTS: Right.

MR. ALLEN: It's not about, or it shouldn't be about simply replacing resources. You know? And I think oftentimes, the private sector is leaned upon to contribute more and more and more, but from a policy standpoint, if those responsible for making funding decisions are not willing to provide the investments for organizations like NIH and FDA to have increased resources, then they simply won't be able to participate in these. You know, there is not a replacement mechanism.

But you know, in terms of checks and balances, I agree with Pam. They

exist. And by bringing everyone together, that will naturally sort itself out.

MS. TENAERTS: Yeah.

MR. ALLEN: And by not doing so is essentially saying that the current environment and the status quo is acceptable, which I think we're all here to say it's not, and we can do better.

MR. MCCLELLAN: Thanks. So, we've had a lot of ground to cover with this panel, and I want to thank you for covering all that ground. We do have a few minutes for questions from the audience. So, if we get the microphones up here, I'll start right over there.

SPEAKER: Thank you for quite a tour de force. One of the things that I find interesting that I didn't hear much about is the shifting definition of health from absence of disease to optimizing health. And it strikes me that the question that people really want answered is, how do I never get sick.

And a lot of the tools that we're getting in sensors and citizen science type activities which don't traditionally fall into the "medicine space," actually have really made strides in the last couple of years that could offer a lot more structured understanding of what health is. But I'm wondering how you think about that in the scale of biomedical innovation, because as a former researcher, I'd definitely put that in there. But this discussion has been more about the treating of disease after it happens.

SPEAKER: True.

(Simultaneous discussion)

MR. CHIN: Well, we could say a lot about that. Clearly, it's a very important point, and there are many, many investigators and groups out there really very interested in understanding what leads to healthier living, longer life. And there are certainly many stories of folks who study those healthy aging individuals who reach a hundred and understand, what is it that -- whether it's genetic, environmental that's sort of helped in this.

I think it's important. They are probably genes. They are not only a cause of disease, they keep you healthy. So, how do we understand more about those and help promote the activities of those genes, shall we say, and not only attack those that actually cause disease? So, there's a lot of activity there. And you'll see more and more as we go along.

MR. MCCLELLAN: Next question back here?

SPEAKER: Thanks to you, Brookings, for organizing this event and to a great panel and set of comments.

The question I had is, all of these initiatives are really exciting. I'm a big fan of the large simple (Inaudible) -- the adaptive designs, the built-in quality by design. All of that is wonderful. But as Mark pointed out, it's really hard, because it's about changing behaviors across --

(Audio skips)

SPEAKER: And the thing I -- or the issue I didn't hear a lot about in this panel are incentives. I'm a big believer -- particularly when you have to have that kind of behavioral change across (Inaudible).

(Audio skips)

SPEAKER: -- expenses and the time and sponsor to do something that is not precedent driven or involves some risk is really difficult for the FDA, obviously as a regulatory (Inaudible). Many of the institutional players, whether they're IRBs or others, have incentives (Inaudible) in this process. Is it patient groups?

And then, you can see why on some cancers, you really have seen that driven that way. Or is it just a reimbursement process, at the end of the day, that we still have a relatively (Inaudible) -- development model. Maybe if that were different, you would see (Inaudible).

MR. MCCLELLAN: Good question. Jeff, do you mind turning to you first, because I think unquestionably, in many of these areas, pressure from patient

groups has made a big difference. And I've heard people say, well, if you could clone Ellen Siegel, for example, in (Inaudible) these areas, we'd see more movement towards getting these collaborative efforts together. But that's a hard thing to replicate.

MR. ALLEN: (Laughter) It is a hard thing to replicate. You know, but I think it's true. You know, there does need to be that driving force to point out you know, really, at the end of the day, what is the ultimate goal. And it does take people to -- it requires people to kind of rise above the challenges that they acknowledge within their own space of some of these partnerships, and sometimes, it's harder than others.

But that's why I think going in to any large scale initiative like this, everybody has to agree, one, we're going to do business differently. But also, what the goal is. You know? And if you can keep focused on the goal, then in many cases, some of the hard decisions that are underneath that, can be taken care of.

Of course, resources and reimbursement you know, is an issue. I think one thing that we maybe didn't stress enough in the discussion today is that the more complex you make a study, the harder it is to actually conduct. And you know, the reality is you know, what we're talking about, at least in the community health setting is you know, patients (sic) that are on single digits of minutes that they spend with a patient. And that makes it very difficult to explain a complex study or implement a complex study into regular practice. You know?

Frankly, we've seen this from the Lung-MAP study, that there are some complexities to this that have made it more difficult for some research practices to implement a study like that. Some of it may, indeed, be resources. You know, maybe not just on single patient reimbursement, but even from a staff perspective of having people with the expertise and the time to implement a large scale study. And this will happen with multiple endpoints. The more you add into the data collect, the more complex it becomes.

So yes, finances is a part of that, but there also has to be the willingness

to change behavior across the board and expect that people can do things differently, if we really want to achieve different goals.

MR. MCCLELLAN: So coupling that change in behavior -- and that's something where patient advocates and leadership can make a difference. Coupled with that, though, is the incentives. So, incentives can maybe go in two ways. There is getting the benefits up and there is getting the costs down.

There have been proposals around providing incentives to participate in research, everything from patent extensions to maybe subsidies or programs like Coverage with Evidence Development in different payer programs, Medicare and elsewhere. But there also have been some good ideas about getting the costs down, making it easier for patients to participate in either real world studies or clinical studies, reducing the cost of clinical trials, as you all have emphasized.

Since, Jeff, we've already picked on you, Pam, Bill, anything to add on most important steps to improve incentives by getting benefits up or costs down?

MS. TENAERTS: I think there's almost, at the moment, the incentive that it's not possible to continue the way we are, so we have to look at things differently (Laughter). And I think everyone is very aware of that, which is why people have come to initiatives such as CTTI and work Friends of Cancer Research, because we have to find other ways of doing things. So, it's almost the reserve incentive that's place that -- continue like this. Got to figure something different out.

And then, the other thing is, there are other ways to make things cheaper. We haven't talked about the use of technology or anything like that, but I think those are also things we're looking at.

MR. CHIN: Really not much to add. I do like the way Pam framed it. I think what we have right now, from the medicines discovery and development perspective is unsustainable. You'll hear in the next panel and remind us that it costs even more in order to produce one medicine, if you count all of the failures, so to speak,

in this process.

The failure is not an admission that you know, industry is not good or the whole system is not good. It's just that that's inherent in a system where we don't know everything. Okay? So, in terms of incentives, I think this is something that I believe is the key to everything, but sort of the reverse incentive. We've got to do something, or else the whole system will break down, is a very important one.

But investment in innovation is costly, and so, there's got to be a way of being able to, at the same time, be more effective in finding the better targets for patient's needs, but also, to think about, whether it's clinical trials -- figuring out how, together, we can figure out better targets to all pursue, and maybe not all pursue them independently, and think of the duplication and the cost involved in that, which in the past, was considered to be competitive advantage, but maybe at the end of the day, it's not anymore.

MR. MCCLELLAN: Well, I want to thank you, Bill, for that -- well, all of you for the answers, but Bill, for giving me my transition to the next panel. You're right. They are going to be talking about some of the numbers that go along with many of the important issues that we've discussed on this panel, so you'll have a chance to get a more quantitative perspective of just how can we go about getting to more definitive evidence on what's working and what's not, to address the biomedical innovation challenges that we've talked about here on this panel.

But right now, I'd really like to thank all of you for your efforts to frame this discussion today. Thank you all very much. (Applause) And I'd like to ask the next panel to come on up to the stage.

MR. DANIEL: Good morning everyone. It's great to see you all here today. I'd like to echo Mark and Alice this morning for welcoming you all to this conversation. And as our panelists on this first session noted, there are just an amazing

amount of unique opportunities that are actually in practice today that can help improve biomedical innovation. What we'd like to do now is turn the conversation to the underpinning data around all of this and ask important questions like how can we harness data throughout the discovery, clinical development and regulatory review to better understand the trends and driving factors towards innovation. Is there a better way to approach these questions? Are we taking a fully informed approach to understanding what the true drivers are to innovation? And also, how can we move beyond simple counts of new approvals each year, to really understand if these policies are having an impact on developing better innovation. And then finally, how can we actually track in the post market environment, to really understand true value and understand if these new innovations and policies intended to incentivize development of new innovations actually result in better outcomes for patients.

So I'd like to introduce our panelists for today. We're going to do it a little bit differently than we did on the first panel because our panelists on this session have a lot of great analyses and results to show you all, so in order to see the slides we'll have each of the presenters come up and then go ahead and sit back down off the stage until all of the presentations, and then we'll invite you up for the panel discussion. But first with us will be Mr. Jonathan Leff, who's a partner at Deerfield Management and Chairman, the Deerfield Institute. After Jonathan, Dr. Murray Aitken, who's a Senior Vice President at IMS Health and Executive Director of the IMS Institute for Healthcare Informatics. Next would be Dr. Peter Neumann, who's the Director at the Center for the Evaluation, Value in Risk and Health at the Institute of Clinical Research and Health Policy Studies at Tufts University. And then finally, Dr. Marta Wosinka, Director in the Economic Staff Office of Strategic Programs at the Center for Drug Evaluation and Research at FDA. So welcome all of the panelists, but we'll start with Dr. Jonathan Leff.

MR. LEFF: Thank you Greg and I want to thank Brookings for hosting this important conference, once again on the state of biomedical innovation. You know I

think this is my fourth year being invited to speak here at this event and I was thinking that each time, remember that each time for the last three years, Mark has suggested that hey, it would be great if we could discuss not only what is the state of biomedical innovation and what should we do about it as a policy matter, but how do we measure it and how can we measure it better? And then I realized that in each of the last three years, I've pretty much politely ignored that request, and really just spoken about the state of innovation and what I think could be done about it. And the reason for that is that I couldn't quite figure out what to say about the question of measurement, other than that existing measures are not very good, but they're what we have to work with. So the good news for me is that Mark and Greg have invited me back this year, despite my persistent refusal to talk about the topic at hand and the good news for Mark and Greg is, and for all of you, I think, is that I am not here today to talk again about my opinions about what to do about biomedical innovation, but I actually am going to talk about the question of measurement. And the reason that I have something to say about the question of measurement is the direct result of a tremendously productive collaboration that our group at the Deerfield Institute has had over the past year or so with our friends and colleagues here at Brookings, on this specific question, where we've set about not only to think about what are the issues with measuring and tracking biomedical innovation but to actually do something about it. And so that's the topic that I wanted to get into today, is what are we actually attempting to do about it.

So the topic I want to introduce today is the project that we're undertaking, as I said, at Deerfield Institute, in collaboration with Brookings, and it is an effort to build a more comprehensive database, tracking new drug innovation than has existed in the past. Just in the way of background, I think, as everyone here knows, there are metrics that are tracked and commonly cited, to assess the health of the new drug innovation enterprise, and in face, my talks here over the last several years, I think, have started with charts like this, that look at, you know as I think Greg just said, one of the

most commonly tracked metrics which is the number of NME approvals, and it's often plotted as it is on these two slides in conjunction with industry investment in R&D. And these two metrics, if you looked at them over a couple of decades on the right, or over the period of six decades here on the left, in all cases, seems to point to a decline in R&D productivity. Basically, we're spending more and more and it's not clear that we're getting more for it, if you just look at the output of new medicines being approved each year. So these are the kind of metrics we have and this is something that people spend a lot of time talking about looking at and it does paint a concerning picture of the state of biopharma innovation. And I think that perhaps the greatest value of these metrics is that it has helped to -- these metrics have helped to get the attention of policy makers and policy makers as I think people here know, and was just discussed in the last panel, are looking for solutions because of the apparent decline in productivity that we're talking about here. I think people here are familiar with the FDA Safety and Innovation Act, or FDASIA, in 2012, where a number of reforms were implemented, designed to enhance the innovation process and accelerate drugs to market. Also in 2012, the President's Council of Advisors on Science and Technology undertook to dig into this and made a number of policy recommendations and as has been said, Congress is now looking at this question in the 21st Century Cures Initiative, through the House Energy and Commerce Committee, and the Senate just this week held hearings on the topic of how to advance biomedical innovation, so there's a focus on the topic. And on the one hand it's a great thing that these kinds of broad measures of biopharma innovation have contributed to a sense of urgency among policy makers. But on the other hand, the dialog about how to enhance new drug innovation highlights the limitations of the existing metrics we have, so while we can say that R&D productivity appears to have declined over the course of six decades, we don't have great data to allow us to answer the kinds of critical questions that inevitably need to come next. So for example, what has caused the decline? Lots of different views and different opinions on that but actually not great

data to get underneath the question, that is the decline more acute for certain classes of drugs, or certain therapeutic areas than others? And what has been the impact of prior policy interventions that have been intended to help address this problem? And then probably most importantly and what is the ultimate question, is, as we talk about new policy interventions, new ideas that sound good, how do we think about and measure what their effect is likely to be and then actually track the effect that they have if we implement them? In effect, because of the state of the existing metrics, we're left with this problem, which is how can we fix it, if we can't measure it? So when our groups at Brookings and Deerfield began to dig into this problem more deeply, we first studied the literature to identify the most commonly cited metrics that are used to track the innovation process. And there are many, such as NME approvals, R&D spending, venture capital investment or other forms of investment, new company formation, FDA performance metrics, people look at review times or first cycle approvals. And then measures attempting to track the cost of drug development through the success rates in drug development. These are the major categories of measures that we found out there that are tracked or attempted to be tracked and talked about. While all these types of metrics have made valuable contributions to the field, we identified some key limitations with them. In general, these metrics painted incomplete picture. For example, like the aggregate measures of biopharma productivity that I showed you at the outset, these metrics in many cases may provide an overall picture of what's going on in the enterprise, but they don't allow for disaggregation to analyze and understand the underlying drivers or what's happening in different components or different parts of the eco-system. We also found that these data sources are often inconsistent or incomplete when you look at different data sources that may be trying to track the same thing or different aspects of the same thing. Some of these metrics, such as cost or success rates of development, are often drawn from surveys, and thus while they provide meaningful information, they may not reflect the full landscape, so they may, for example,

track what's happening in big pharma but not what's happening in smaller biotech companies or vice versa. And then of particular importance, many of these metrics are not routinely collected and updated. What you find in the literature is that an individual researcher or group of researchers assembles data from a bunch of different places to try to answer a specific question. And then they're able to say something interesting about that specific question, but the underlying data then that was created quite laboriously by those individual investigators, is not frequently maintained and is not available for future analysis. And then even when it is, the underlying data is often not publicly accessible to future researchers who may want to build unpublished analysis or dig deeper. So we have quite a fragmented system and one that requires actually an enormous amount of resource, of individual researchers to answer questions that one would have wished could be answered much more easily and as a result, there are a lot of questions that simply go unanswered.

So our teams at Brookings and Deerfield set out to create a comprehensive database of key development, regulatory utilization and outcomes characteristics of each new drug that's been developed over the last 20 years, and we're doing this because we thought, wow, that should be out there and if it were out there, a lot of these questions could be answered with empirical data and answered much more easily than they can be today, but it's not out there, so we said, let's set out to do it, with the goal of enabling not just ourselves but the entire research community and people who are interested in the topic of innovation to be better able to measure it and better able to interrogate the data to think about what the impact of different kinds of policy interventions might be.

So we published the rationale for this project and the basic architecture of our proposed solution, this database, in Health Affairs last month. And the primary objective of the project is to develop, populate, maintain and make publicly available a comprehensive repository containing key metrics of new drug development, utilization

and impact. Now we recognize this is a big and ambitious project and we have lots of ideas for it, so of course we have to break it down into stages.

These slide shows, on the left are four proposed research categories and some of the initial data elements that we intend to populate in the database on the right. And I apologize for the eye chart here. I won't have time to go through this in detail today, but these exhibits are taken directly from the health affairs paper so you can refer to them. The main points that I want to draw people's attention to here today is that first, we ultimately want this to be broader than just looking at the development characteristics of new drugs. That is where we'll start. We'll start by looking at key development characteristics such as development time and clinical trial size and regulatory aspects such as different regulatory pathways, to be able to look at how all those things interact with the health of the innovation enterprise. That's where we'll start and that's really perhaps the low hanging fruit for drugs that have been approved by FDA over the last 20 years. That's a big project in and of itself but we do intend to go beyond that. That's really research category number one, phase one. We intend to go beyond that and look also at measures of new drug utilization and outcomes, and also at drugs that fail or are abandoned in development, as well as those that are approved. And finally, at broader macro or system wide kinds of factors that affect the innovation process.

The second thing just to highlight here is that we know that what we're talking about here is a big effort. It's a big project and it's a vision and it's not something that's going to be completed overnight, and will be developed in stages and hopefully those stages will be useful to the community to conduct analyses as we build it, but this is really a vision for something that we hope to create and build upon for many years to come. So how are we going to make this a reality? The first step is the commitment to do it. Brookings and Deerfield have developed the concept with input from a variety of stakeholders and we're now committing substantial resources to it.

Second step is collaboration. We are looking to build a consortium of

stakeholders who share this vision. A third step is to access the right expertise. We need to build a consensus around exactly what metrics are important to collect and what's the best methodology for doing so. And fourth, we want to get this right. So we intend to make the necessary investments up front in data sourcing and development in order to ensure that the database is ultimately as accurate and as comprehensive as it can be.

So finally, where do we go from here? I just want to close today with the call to action. We need everyone's help. We at Deerfield and Brookings can't do this alone, and we don't want to do this alone. We want collaboration across the entire community. To start with, we want to engage with key stakeholders who have an interest in this project and who can contribute thought leadership around how best to do it, how best to design it and architect it and what the questions are, that we should make sure we can answer, when it's done. And stakeholders who can help us find and access the data sources to populate this and make it all come together.

And then finally, or additionally, we're looking to establish expert groups to build consensus on research questions of interest and to help us design the database and to create definitions of data elements, because you often find that some of these things are not totally objective and require expertise from different fields within the community to be able to designate a given field for a given NME. So this is a call to action. We hope others will join us and we'll be able to build a database that will ultimately be publicly available for analyses to try and empirically get at the kinds of questions we're all talking about here about how to make biomedical innovation work better. Thank you. (applause)

DR. AITKEN: Thanks, good morning. I'm Murray Aitken from the IMS Institute for Healthcare Informatics and I'd like to spend just a few minutes taking you through three examples of research that we've been involved in, at least a couple probably fit on that left hand side of Jeff's chart where there are limitations to what we're

able to see, what we're able to report out on. And indeed, in the context of Jeff's comments, these are the sorts of areas where we look forward to being able to contribute to a broader effort to get our arms around this important issue of measuring the health of the biomedical innovation system.

The first thing I want to talk about is a piece of research that was published in Health Affairs last year, last month. Lead author was Ernsburn from MIT, and this at some level was trying to connect the issue of what's been going in to R&D budgets and expenditure and what's been coming out in terms of economic returns for that investment. And at some level, this sets the bookends of the innovation ecosystem and so what we sought to do was update some of the earlier work that's been done, looking at the economic returns from investments in biomedical innovation by the CBO, by Grabowski and Vernon from the 1980's and 1990's and a little bit the last decade, and what we were able to do was create a data set of 466 new molecular entities launched between the period 1991 to 2009, and look at what the commercial returns have been for that set of innovation. About 80 percent of the new molecular entities were small molecules. About 20 percent were large molecules and what we were able to do was look at the lifetime sales for each of those molecules, where we defined lifetime as the period from launch until patent expiry plus 24 months for small molecules plus 60 months for large molecules. We did the analysis starting with the U.S. market and then applied a multiplier for global markets. We converted everything to 2005 dollars and created a net present value so that we could see what have been the trends during that 20 year period or so in terms of the lifetime sales of the new molecular entities. And this is a summary of the findings. So this is the average net present value of the lifetime global net sales of the novel act of substances in NME's in four different cohorts. So we grouped around four to five year periods. And you can see from this that for small molecules, the average present value was 3.3 billion in the first period. It rose to 4.2, 4.8 and then a reasonably significant decline for the cohort of new products launched in the 2005 to 2009 period.

For biologics, a stronger net present value or higher net present value and particularly high in the 95 to 99 period which was a time when some very remarkable innovative biologics were launched and came to market, but then a fairly steep decline since that point and in the most recent cohort, a lifetime sales of 2.7 billion. So the blue takes that combination, showing the average and again, what is catching our attention of course, is being what's happened in that most recent cohort period where the average net lifetime sales has declined.

Now again, this is a good example where we can measure what's happened, getting underneath that and looking at the drivers of that change is more difficult, although we do have a very detailed database to work with. Things like orphan drugs for example, which have become a more significant share of the new molecular entity launchers, on average carry a significantly lower net present value of lifetime sales than do non orphans, not surprisingly. So as that percentage of drugs coming through, as orphans increases, not surprisingly that's one of the reasons we see the downward trend. We also know there's been a lot of a change in the commercial market for new pharmaceuticals, heightened competition, growing consolidation of purchases, a growing scrutiny, indeed, by payers, as to the value that they receive from new drugs. And we do think that those factors have been having an impact on the lifetime sales trends.

What we also wanted to do then was link that lifetime sales to the costs associated with the development of innovative biopharmaceuticals in order to derive an economic return. We used an 11 percent discount rate for small molecules, 11 1/2 percent discount rate for large molecules. We used the Tufts average cost of bringing a new drug to market over this period. We used operating cost metrics from the literature, and so when we combine all of that, we end up with a net economic return which as you can see was relatively strong in the earlier period, particularly for biologics notably. But importantly in the most recent right hand cohort, 2005 to 2009 launches, we actually see on average a negative economic return, again, using an 11 percent discount rate for the

average of the drugs launched in that most recent period. So this is one of the issues that I think a lot of people look at and they -- what does this mean for the sustainability of investment into the biomedical innovation, if there are in fact no economic returns. You know, this is also the sort of analysis that from our perspective doesn't get looked at as closely or as frequently as it should, to understand whether in fact we have that right balance of incentives for capital to be put at risk and into investment in biomedical innovation.

A second piece of analysis we've done is to look at what's happening in the pipeline of preclinical products, so we maintain one of what Jeff would refer to as a less than perfect database, although I would say it's consistently imperfect, which means the longitudinal view can be relevant where we seek to identify all of the products in both preclinical development as well as clinical development. And here, this is just a snapshot of what we see coming out of our database. This is looking at the number of preclinical projects where there has been activity within the prior three years, which is an important caveat but one of the complexities of measuring things is knowing when something is really dead and when it's just dormant for five years, ten years or longer. But for the sake of this analysis, we simply looked at products that at each, at the end of each of these three years, was in preclinical development and had been active within the prior three years. And as you can see, it's a significant decline from about 5800 at the end of 2004, to 4700 at the end of 2009 to 2000 at the end of 2014. Again this is a good example of, well these are the numbers, but what's really going on underneath that, and again, I think this is where there's still a gap in being able to pull this together and do a more causal analysis of what's really going on here, and whether indeed this is good news or bad news, because it's a little hard to tell simply from the numbers. This also speaks to the growing importance of oncologics in preclinical development. That's the orange bar in the middle there that's, while it's down in absolute terms, it's increased its share of the total activity going from about 29 percent to 40 percent over the past decade. CNS,

central nervous system projects are now 16 percent of the total and anti-infectives are about 20 percent of that total.

The other thing we looked at is who's bringing these preclinical compounds into the pipeline and what's the role of big pharma in that? What we've seen is that the 20 largest corporations in biomedical innovation have reduced their share of the preclinical compounds over this 10 year period from about 15 percent of the total to six percent of the total. Again, this is one of those facts that I think we should be able to talk about in terms of whether this is a good thing, a bad thing, and what the underlying drivers are.

Just finally and very briefly, we've also been looking at the average time for clinical development to occur from stage to stage, and here we're just presenting the averages of products moving from phase one to phase two, from phase two to phase three and from phase three to submission, in five year cohorts. And then we've divided it between what we would call traditional therapies, mostly small molecule, more primary care kinds of therapies and those that are specialty, more biologic and so on. And again, the trend here is one that shows a lengthening of time for products to progress from stage to stage, so from phase one to phase two, the average in the most recent five year cohort, 25 months, up from 18 months in the 2000 to 2004 cohort, 36 months for phase two to phase three, 36 months phase three to submission. Again, these are the top line numbers. We have about 500 in the 2010 to 2004 cohort for each of the phase changes, so it's a reasonably good data set and one that could be subject to a lot more analysis, again, to try to get under the surface here and say, what's really going on, how much of this is related to policy changes, how much of it is related to the economic factors we've talked about and the other changes that are occurring in the environment.

So let me stop there but you know, again, we are very supportive of the idea of contributing and participating in efforts to bring together what really does look like a very disparate set of information that is around and about, which doesn't come together

in a very easy way to date, so that we can have a much deeper understanding of the health of our biomedical innovation system. Thank you. (applause)

DR. NEUMANN: Well good morning to all of you. I'm Peter Neumann. I direct the research center at Tufts Medical Center in Boston. Thank you very much Greg and Mark and Brookings for inviting me today. People have been mentioning this 2.6 billion dollar figure that comes out of Tufts. That's a different center than mine. Its colleagues and they do great work. I direct a different center. And we've been in our own way, trying to quantify value and innovation, so in my brief time, let me share with you some of the data that we have and tell you how we're trying to go at this. So three basic research initiatives -- one, the Tufts Cost Effectiveness Analysis Registry, some of you may know a database of cost effectiveness studies. Two, a database of quality gains -- these are quality adjusted life years, a way of measuring population health. I'll share with you some new findings. And finally, we've been tracking all of the Medicare national coverage decisions over the last 15 years or so, and we have a database of these and it's another way of getting at how evidence is translating into coverage and reimbursement decisions in a window into the innovation process.

So first, the Tufts Cost Effectiveness Analysis Registry, there's our web site. It's a publicly available database, at least we make a good chunk of the data publicly available. It's a database of cost per quality studies, okay, so we read through the vast medical literature -- the peer reviewed Medline literature. We collect data on every cost per quality study as it appears in this literature. We collect a lot of information, we standardize it in various ways including in 2012 US Dollars and put it into a database. So this is the only math on the slides today. In the numerator of these ratios is the delta costs, the changing costs that result from investing in these technologies. I'll give you some examples in a moment. In the denominator is qualities, changing qualities. And the delta is because all of these interventions are being compared to something else, status quo, next available, best available alternative. So you can, and let me just say,

there are challenges with cost per qualities. We are well aware of them. We've written about them. The great strength is it gives you one number that captures morbidity and mortality in a single ratio reflective of value. With any single number, there are always questions about whether you're capturing well what people care about. Nonetheless, what you can do with these ratios is array all kinds of innovations and technologies and therapies, diagnostics, procedures, on a graph. So unless that cost saving and health improving and these are just examples, we have 11,000 of these in the database. Some are older and probably not as relevant, but you can search and find vaccination against chicken pox of infants. One study found, this was cost saving. It saves money because you offset enough cost to offset the cost of the intervention, a vaccine. And as you go up the scale, 20,000 per quality, so now it's in a way costing us money, costing society money, for every quality adjusted life you have gained or produced, its costing 20,000 dollars in an aggregate term. G&SA guiding chemotherapy and breast cancer patients, and as we go up the scale, it's becoming more expensive to buy units of health, in other words, less efficient ways of investing in innovation. Senility, everyone's poster child for high priced medicine, actually shows up at least in some populations as fairly reasonable value for money. Most people, and this is a debate and controversy we can come back to, most people would say 50,000 per quality is under conventional standards, pretty good value for money. Now, you know, that's not to say this is not a big budget item for the payers, or not controversial in other ways, but if you simply look at the return on what you're getting in terms of the cost per quality, so (inaudible) in HCV, Hepatitis-C, that is fairly cost effective. Sixty-five year old men, screening for osteoporosis, less cost effective, lung volume reduction, surgery comes out as even less cost effective. You get the idea. Recently Medicare covered CT screening and lung cancer shows up as you know, fairly good. All of these ratios beg questions about which population and which comparator, and on and on. A lot of that detail is in the database, but you get the idea. It's a way of quantifying innovation. It's a powerful construct.

Okay, let me turn briefly to quality gains. Out of the denominators of these ratios, you get a measure of population health effects, quality gains. And again, it gives you one number to quantify value and innovation. And so my colleagues and I have been doing this in various ways. We had a paper last fall in Health Affairs which looked at specialty drugs versus traditional drugs in terms of quality gains. And what you see and you can read the paper for details, but a lot of the specialty drugs, despite high prices, which are real and in many ways, eye-popping, the drugs actually do pretty well in the quality gains. In other words, they seem to produce pretty robust health benefits, at least compared to traditional drugs. And furthermore, if you actually then look at the additional costs and quality gains, the results are somewhat complex and nuanced but a lot of the specialty drugs do pretty well. Not all, you have to read the paper. It does depend on the specifics, but again, it's a way of quantifying value and innovation.

So this is brand new data. Never was before seen until right now, except by Mark McClellan. So we stratify the quality gains by FDA approvals over the last 15 years, since 1999, given the FDA designations in different categories, so FDA designates certain drugs as fast track, accelerated approval, priority approval. We had 102 -- the reason we had 102 is we could not find what we thought were good quality estimates for all drugs, so the 102 represents about 40 percent of all drugs that came through FDA since 1999. And we stratified by, first row, fast track versus fast track, and looked at the quality gains of the fast tracked drugs. What you see, and you see it also in the second and third rows for accelerated approval and priority reviews, but at least by this metric, FDA seems to be doing pretty well, you could argue. In other words, it's discriminating products that seem to have larger population gains according to these quality estimates versus products that go through regular review. And again, this is -- it's a rather you know, well, a bit of a complicated story and analysis and begs you know, probably a full scientific abstract and discussion, but, and it's not yet published, but it's another way of trying to put some numbers around policies that we are implementing and so we're

excited about it and we're going to push it and eventually we'll publish it.

So finally, let me turn to another stream of research that we call predicting coverage. So we've written a number of papers. There's sort of a perspective paper we did, my colleague James Chambers and I, who also was behind some of the other work. Medicare and for that matter, all payers have this ongoing challenge, right -- new technologies come along. They must make a decision and for Medicare and you know, I guess every payer has a version of this; it's a determination of whether the new innovation is reasonable and necessary. That's actually statutory language for Medicare as most of you probably know. So we have put into a database all Medicare national coverage decisions. These are exceptions. Medicare makes most decisions at the local level or Part D plans make their own determinations subject to Federal rules, but sometimes Medicare makes these national coverage decisions -- lung cancer screening, colorectal cancer screening, certain Part B drugs go through this process. So we call this playing money ball for coverage and reimbursement, in the sense, you know, money ball, trying to quantify in baseball and other sports now, with all kinds of statistics, how decisions reflect all kinds of variables. So we've been developing statistical models to try to understand, is Medicare -- has Medicare been consistent? And the answer seems to be yes, more or less. Is the evidence bar getting higher over time? We had a paper last month in Health Affairs which really strongly suggests that the answer is yes, that technologies which might have been covered 10, 15 years ago; the same evidence would not be covered now. And it's not necessary that CMS is sort of you know, tightening up because of fiscal concerns although probably they are. It may well be that Medicare is just becoming a much more sophisticated consumer of evidence. They're scrutinizing the evidence more tightly. There are other analyses that come out of here as well, and I could share some of that with you. But again, the common theme is, we can talk and we should talk about policies or innovation and measuring value, but through efforts like the two previous speakers mentioned and I hope, you know, these efforts, we can bring

some empirical basis to it.

So I'll just end on you know, we should focus on value of course, not just costs, and that is sort of a, maybe, in a way, a kind of throwaway line, but I think it means really measurement and we can do it. We can quantify innovation and value with a lot of limitations, but we can do it. And the answers, you know, will depend entirely on the specifics, that you can't say new technology is good value or not. You really have to do the studies and make the case and show the data. The information I think can inform decisions, but as lots of other speakers earlier today, and Mark, emphasized, it needs to be combined with changing incentives throughout the healthcare system. So thank you very much. Look forward to your questions. (applause)

DR. WOSINKA: Thank you very much for having me here. And today's presentations and in some of the discussion earlier, I heard the benefit risk assessment mentioned several times and also I've heard references to the therapeutic context, which is what I was going to talk about even though people didn't really call it by its name. In my talk what I will do is, and we -- I need to advance the slide, sorry -- in my talk I will talk about -- I will try to explain the concept of therapeutic context, show how it relates to trial design and timing and by extension, to the cost of drug development.

But first, a necessary disclaimer, that the views expressed in this presentation are mine and do not necessarily represent an official FDA position. I should also mention that my talk is really about science, and I am an economist. So I will try to take a birds-eye view on some of these issues and with that, I might not, I might miss some of the nuance that's involved in the regulatory decisions, and just evaluation of science.

So first I think it's useful to sort of ask, how much is the cost to develop a drug? And you have heard one number, the 2.6 billion dollars. But really, the reality is that it actually varies greatly. So this is from a very recent study by Deloitte and they studied 12 biopharmaceutical firms in three different year cohorts. And what you see in

this picture is that there's tremendous difference in the cost to develop an asset from discovery to launch, across these 12 companies. And what is captured here is both the direct cost of the developing that asset as well as the cost of the failures. And what you can see, the range is from less than 400 million for firm B, to firm D, I don't think you can really see -- yeah, you can see here. Firm D, over three billion dollars to bring one asset on average to market. So what's going on here? Sorry, just got moved. So one thing that's going on, and this is actually that article that report actually gets into, is that some of it is driven by differential R&D productivity. There is growing evidence that small biopharmaceutical firms are more productive than large biopharmaceutical firms, meaning that they get more successes for the amount of money that they spend. What I would like to focus on is to what extent -- to really talk about the variants that are related to the kinds of drugs that these companies are developing, and the therapeutic context that surrounds that.

So what do I mean by therapeutic context? What I mean by this is what the disease is, why it is the way it is, and how we currently treat it. And these three are really highly interdependent but it is really useful to look at them one at a time. So why is therapeutic context relevant? It is because it is really the context for the regulators' determination whether the drugs' benefits outweigh the risks. And therapeutic context says implications for R&D because it influences study design. It will determine the end points. It will determine the choice of comparator, the entry criteria, the trial size and the trial duration. It may also influence the timing of trials. So it can help answer questions like, can phase one studies -- can they be combined with phase two? If early development establishes effectiveness, efficacy, can and NDA be submitted without completed phase three trials?

So let's look at the what. What I mean by this is the characteristics of the disease. So how the disease presents itself can really influence the trial design. So for example, chronic and episodic conditions require, in general, they require long studies if

no surrogate end points are available. It just takes longer to wait for the outcome to happen. Also, for example, does the drug try to prevent an infrequent event? If so, you will need a large sample size simply to gather enough adverse outcomes to be able to compare it across the different study arms. How the disease presents itself can also influence the timing of trials. So for example, phase one might be combined with phase two if a drug is expected to have toxicity that's unacceptable for health volunteers. And this is actually something that happens often in oncology drug development. In some circumstances the regulator may be willing to work through the drug without completed phase three trials if the drug establishes efficacy earlier, in earlier trials, and the drug treats a severe condition with few ordinal treatment options.

So the next step is the scientific knowledge, the why of the therapeutic context. Why is the disease the way it is? What is the mechanism of action for the drug? What is the causal pathway of the disease process? So understanding the disease pathophysiology biochemical and genetic underpinnings of disease helps number one, directly lower cash costs, if companies do not have to do such research in house. It can lower failure costs by pointing out dead ends and as Bill Chin actually mentioned earlier, quoting here, we have a lot of failure costs because we don't really know everything. So this is where knowledge actually can really increase the set of the success rates. And this is where, why having such information in the public domain is really important. The why can help us identify which people are likely to respond or not to respond to the drug, or which ones are likely to experience side effects? So in terms of trial design, knowing who will positively respond often comes with a higher magnitude of effect, which means you might not need as large of an end of a sample size.

It can also cut trial length by helping to establish the causal pathway of the disease process and therefore identify surrogate biomarkers. So Alzheimer's I think is a very good example of that last point. So the what of the disease makes it very difficult to study, to develop drugs around. It's a disease -- it you lose brain cells, there's

really not much you can do, so the focus shifts understandably towards prevention and maybe slowing down the disease. But the disease progression takes many years, so again the what makes it even on that, and really hard to study, and therefore you would have to have really long trials unless you have surrogate biomarkers. Unfortunately we don't really have a full understanding of the disease pathway and therefore no appropriate surrogate end points have been identified for the disease. On the other hand, you actually have some great success stories, so if you -- that really paved the road, the way to many important therapeutic innovations.

Just consider the payout that we have received on building the scientific infrastructure in HIV and cancer. And as a matter of fact, there are spillovers to other therapeutic areas from the infrastructure that was built, so for example, the advancements, the recent advancements in hepatitis are very much benefitting from all of that infrastructure that was built in HIV.

So what I wanted to do at this point is to -- no, I skipped a slide somehow -- hopefully I didn't skip it earlier. All right, so the very last component is the how of the therapeutic context, and what I mean by this is how the disease is treated, or the existing therapeutic options. Therapeutic options determine the extent of the medical need for a given indication, so it is -- and that's exactly where it becomes relevant in a benefit risk context. So think about AIDS 20 years ago and now. The extent of our medical need has really shifted. So this is actually interesting. This is the aspect of therapeutic context where we can become victims of our own success. Some conditions have established standards of care with existing therapeutic alternatives and in those cases, trials could not be done relative to placebo, because withdrawing effective treatment from patients would actually be unethical. So if a standard of care is effective, they can really set a high bar for drugs that would try to compete with them. And so in that case, the need to establish superiority or non-inferiority will drive the sample size up.

So what I would like to do at this point is help you visualize the

therapeutic context in the clinical development process. So what I'm going to show you is three examples of drugs in clinicaltrials.gov and this is basically a mock up to help you understand what I will be showing you. So what you will see is the horizontal bars are going to be the different trials that are reported in clinicaltrials.gov and keep in mind that not every trial might be reported, and the colors represent the different phases. The gold circles are the pivotal trial, so those are the ones that are being used to support the submission and the A submission. The black line, the vertical black line is the NDA approval date, and you can actually see the timing from relative to that. And the dashed line is the NDA submission, all right? And one thing to mention is, in all the three slides I'm going to show you next, the scale is going to be the same, so whatever differences you observe, in terms of the size of the trial, or the length of the trial, is all on the same scale. So first let me talk about Brilinta. So Brilinta, what you see here on the left hand side is a study with over 18,000 patients. Brilinta was trying to establish, they wanted to establish that they can reduce the rate of specific cardiovascular events in patients with acute coronary syndrome, or ACS. So the sponsor used a pretty standard end point for cardiovascular studies. It's a combined end point of cardiovascular death, stroke and heart attacks. So all the studied patients have ACS, but only, we expect maybe a fraction of them to actually have one of these events, maybe ten percent. So to deal with this you really have to increase the size so that you can get enough of the adverse events to compare it to the control arm of the study. Another reason that's driving the large study size is that the sponsor's trying to establish superiority relative to Plavix. They are looking for a possibly really small improvement in efficacy, maybe a couple of percentage points at best. To find that small of an effect, they have to power the study and they have to really increase the number of patients by even more so. Then the drug gets approved, and then they look for another indication, same end point, but a different patient population. Because the baseline rate of adverse events in that population is lower than you may see as, you have an even larger sample size.

So now let me show you something on the very opposite end of the spectrum. This is Blincyto. It is a poster child for an accelerated approval drug. This drug was thinking an indication to treat relapsed, patients with, relapsed patients with acute lymphoblastic leukemia, or ALL, which is a fatal disorder. Historically the response rate for these patients to single drug therapies is really poor, about five to twelve percent. Using combination therapy with sometimes up to five chemotherapy treatments and a stem cell transplant, the remission rates improve to maybe 25, 46 percent, but even their median survival rate is about three to six months. So given the really dismal prospect that these patients are facing, it really didn't make sense to do an open label single on trial, which is really a trial where all the patients get the drug. The complete response rate for this trial was 32 percent which is significantly better than any other single drug. The outcomes were about the same as with combination therapies, but taking one drug was sure better than having four to five chemotherapy drugs and maybe a stem cell transplant. So given this therapeutic context, it really -- the benefits of the drug appear to have outweighed the risks with that study alone. And so the drug got accelerated approval without phase three studies completed. Those phase studies continued on and they are used as a -- contribute to be used as confirmatory studies for approval.

The last thing example I want to show you is Sovaldi. The picture here looks a bit different. So one, is because Hepatitis C virus is now very well understood, drugs can be designed to target specific steps in the virus lifecycle. And so presumably you would expect potentially a higher magnitude of an effect if you really understand the disease. So what's striking is the number of studies that they conduct here. The reason is that they design studies to show efficacy across several different genotypes of hepatitis C and they also are stratifying on the patients' prior experience with interferon based therapy. Also they needed several studies to establish the appropriate duration of treatment. They could have done this probably with one, but the sponsor chose several.

So the very last thing I wanted to show you is a summary of just one

metric related to drug development, and that is enrollment in pivotal trial. So again, the pivotal trials are the adequate well controlled studies. And this is the total patient enrollment in the studies that were supporting the different submissions. As you can see, and perhaps this is not a surprise, you see a large variation across these different therapeutic areas. But I think what you might be more surprise by is to see the tremendous variation within some of these areas. But what's going on here is again, is the therapeutic context. So these groups, these drugs, are not homogeneous when it comes to the therapeutic context, so some of these drugs in a given group are trying to prevent a low probability outcome and some don't. Some of them we have an understanding of the disease and we can identify responders and in some we don't. With some of these drugs in the class, and I don't know how this possibly happened, all right -- with some of these drugs in the class, we have good treatment options and with some we don't.

So I guess this is what I wanted to offer as a thought, is that the implication for researchers is if you're thinking about, if you're trying to understand the cost of drug development, the drug development timelines, you really have to account for the therapeutic context, for the what, why and how is it treated currently. And if you were to ask me what are the implications for policy, I would say the what is given, we can't control it. The how we treat it is given right now. The only element out of these three is the why and that's something's that the only area where we as a society have control. So I wanted to end with that. Thank you. (applause)

MR. DANIEL: I'd like to thank all of the presenters and invite them up to the panel. I know we are running over time, but we will spend about 10 or 15 minutes for the panel discussion and while you're getting mic'd, I'll at least try to jump into some of the questions, so listen as you're getting mic'd. We did hear a lot of interesting results. Murray started off with some, not necessarily depressing results but he did paint a picture of the fact that we are seeing declining lifetime sales, potentially negative economic

returns after tax, decreasing in preclinical activity, so this sort of says to me that there's a problem. But then we heard from the other panelists that well, it's not that straight forward. It's very complex to really understand necessarily is that a bad thing and what's really driving that, so what I would like to ask all of the panelists is one question and then I will turn it over to the audience. But quite frankly, what does the data tell us and what should we be measuring? So this morning we heard on the first panel a lot of ideas on improving clinical trial efficiency, about the potential roles of overall evidence development and the importance of bringing in patient perspectives. Is that anecdotal? Are improvements in those areas anecdotal? You all are experts in the data and can help us understand, are those the right focus areas, based on your experience with your data and looking at what's really driving innovation, what we talked about this morning and a lot of the proposals that you might have seen and the 21st century cures -- are those the right areas based on what you're seeing in the data? Murray, do you want to?

DR. AITKEN: I would say they are good areas to focus on. What we need to know is, what we need to be measuring though, is what impacts that they are having and put that in the context of I think, what Marta took us through, which is the nature of the area of research, because clearly things differ dramatically depending on where that focus of innovation is placed. So you know, I think this speaks to the need for us to be able to systematically look at these areas, look at their implementation, and be able to measure what's actually happening in terms of the level of improvement relative to the innovation in different therapeutic classes.

MR. LEFF: Yes, so I would say that when you listen to the public policy discussion and the debate around what to do to improve biomedical innovation, that the answers fall into certain consistent categories, and they're the same ones year after year after year. The details of proposed solutions may differ, but they're the same basic points that people are trying to influence in the system. They'll talk about proposals to reduce the time that it takes to develop the drug or reduce the cost and people talked a lot about

that on the first panel with respect to clinical trials and the inefficiencies that maybe we can design out of our clinical trials, but time and cost are always very high on the list. Incentives that people always talk about, patents, exclusivity, regulatory exclusivity and how do we create better incentives for these investments to be made? And then of course, money, money for research, more dollars are always better. And so the solutions fall into a consistent set of buckets and there's no doubt that those are the right buckets, if you want to drive more innovation, you want to make it happen faster, you want to make it cost less, you want to make it more valuable to the innovator, to innovate and that will drive more investment in innovation and more output through the system.

But the real challenge is differentiating among the different proposals that come about to try and move each of these things, and probably just about all the proposals that are out there will have some positive impact on one or more parameter in the system, all of them also have some costs. You know, they cost money to the system, maybe they're imposing more burden on FDA and that has costs or will spill over to other aspects of what FDA does, or obviously extra exclusivity costs the system money in paying for drugs. So figuring out which ones to prioritize, which ones will actually work, which ones will have a benefit that will exceed the costs associated with putting them into place, is where we start to struggle, and that sort of leads me back to the whole discussion we're having here on this panel, is how do we get our arms around measuring and assessing the impact of each of these kinds of policy interventions or figuring out are we intervening at the most impactful spot in the system. So that's really where I hope we can go and sort of synthesize a lot of the kinds of different inputs that we all talked about here, and put it together in a way that allows the community to ask questions that we're not even thinking of up here but shed light on all these policy issues.

MR. DANIEL: Marta?

DR. WOSINKA: So what I would say is sort of going back to the concept of streamlining clinical trials, when you look at clinicaltrials.gov, what you see is when the

trial started and when it ended, and it's really hard to tease out how much of the length of the trial is driven by the therapeutic context and how much of it is driven by inefficiency in the system. So for example, it is true that with cardiovascular drugs, it's not as hard to recruit patients into these. Probably what happened with Sovaldi didn't have many problems. But with the cancer drug that I mentioned, they probably had a lot of trouble doing this. It actually would be really interesting to go back and try to adjust for the duration of treatment, sort of take the clinical trials that were designed and then also actually look how long the given patient had to be treated and then to see how much of the difference is, and that would capture the inefficiency in the system in a sense. So that, I don't know that that has been done, but I think it's do-able.

MR. DANIEL: Peter?

DR. NEUMANN: I guess I would just add that there are a series of policies that we might put under, to oversimplify, informational policies. So better information for the decision makers, giving them information on value, public and private, and cost effective, mini-sentinel you might argue is informational. The clinicaltrials.gov possibly you put under there. Cover your evidence development, collecting additional information, that is information without necessarily changing regulatory processes or incentives, which is the second big category, which is harder and probably more impactful and I think we need both, but you know, at least I hope from this last session, there's a lot more we could do on the information side, measurement, tracking, providing that information to inform policies.

MR. DANIEL: Yeah, a lot of the proposals are in fact intended to improve efficiency of clinical development to get promising therapies to patients sooner, but implicit in all of that is that we are developing therapies that are impactful to patients and that mean something to patients. And we do a very bad job I think, it's been clear, of really measuring that and cost per quality, qualities, and increases in qualities, is an important measure, but it's hard to do. So my question, just stemming off of that, how

hard is it and are there potential other ways or different ways of measuring qualities that can be more widespread, more incorporated into the learning of patient experiences as we go along, once a product is approved?

DR. NEUMANN: Right. Well certainly there are methodological challenges in measuring qualities and cost per qualities. You know I don't think they're insurmountable of you know, compared to many other things we measure, terribly sort of burdensome. There certainly are other metrics we would like to have alongside those. There are lots of ways to measure health, instead of qualities we can measure life years, we can measure with disease specific metrics. We can measure costs and consequences and leave it as sort of disaggregated information and not put it into a ratio. There might be lots of other information we would like to add to the cost per quality ratios. Cost per quality as I think everybody knows, has been controversial. It raises the specter of rationing. It involves some strong assumptions and so forth, but implicitly, we're making decisions. And we are spending our money to, and allocating our resources, given constraints, so we either use information like cost per quality and other metrics, or we don't. But we're still making these decisions, so you know, I'm a great advocate for information like this, but by no means is it the only metric to use, because there are others.

MR. DANIEL: Any other comments on that point?

DR. AITKEN: I would just bring it back to the patient role in contributing to the definition of quality or whatever the particular metric is and I recognize it's at least implicitly already part of the quality measure. But I think as we hear more discussion about the patient role in reporting outcomes and defining outcomes and so on, it may be a good opportunity to also reframe part of the quality metric to reflect that patient input.

MR. DANIEL: So with this, I'd like to turn it over to the audience. We have a question in the back.

SPEAKER: My question's for Marta. Thank you for a very interesting

presentation. But I want to make sure I understand one of the points that you made. It sounded like as treatment gets better, if you want to then have an additional treatment, you're going to need a larger clinical trial. And if that's the case, then you would drive up, as you get better and better treatments, the costs of additional treatment will go up, right, so eventually that will A, drive the costs of treatment up, and also the return on investment will go down, so ultimately it would sort of cut research off. Was that the implications of what you were trying to say?

DR. WOSINKA: No not necessarily. I mean, if the alternative is really good, and that's the baseline from which you are going, if you're comparing it to a sugar pill, versus if you're comparing it to an effective therapy, then you're looking for small effect. If you're looking for a really large effect, you don't need a large sample size. If you come in, you know there are existing therapeutic options for Hepatitis, but you know they were probably expecting a really large magnitude of an effect for the results because they understand the science of this sort of -- they understand how the drug works and so on. So that's not necessarily one direction in how that goes. But if the treatments are effective and you're just trying to squeak out, from a statistic -- it's purely statistics. It's, if you want to show statistically that you are having a statistically significant difference and the difference is going to be tiny, you will have to have a large sample size to do that. That's a reality of statistics.

MR. DANIEL: I think that's all we have time for questions, so I'm going to go ahead and wrap up this panel. Thank you to all of the panelists for your great comments. It's excellent data. And I'll turn it back over to Mark for just some final comments. Thanks.

MR. MCCLELLAN: Thank you all very much. I'm going to be very brief, so you can just sit tight for a second. We've covered a lot of ground today. There are obviously a lot of unresolved issues and challenges in biomedical innovations but a huge amount of interest and a huge amount of activity in trying to address those challenges. I

was particularly impressed with the work of the last panel in describing how to put some measures of progress on the efficiency of the biomedical enterprise, and the productivity of the biomedical enterprise through the development stages, the cost, the revenues, the value of treatment and how all of these are influenced by therapeutic context, so this in turn provides a way to help guide further policy development. But as you heard from the last panel, there is still more work to do to connect the two. I'm very pleased to see the progress though. So we've covered a lot of ground today and I just want to end by thanking all of our panelists in this session and the first session for framing the big issues in biomedical innovation. We are obviously, like many of you in this room, and joining us online, we are going to continue to be working hard on these very important issues for protecting and promoting the health of the public. I'd also like to thank the staff at Brookings who helped put together this event. You all have already heard from Greg Daniel, but also Serena Codes, Matt Longo, Christina Flores, Joanna Classman especially, Morgan Romine for an extraordinary amount of work to get this event together. We look forward to seeing all of you again soon and look forward to more progress in improving biomedical innovation in the United States and around the world. Thank you all very much. (applause)

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I, Carleton J. Anderson, III do hereby certify that the forgoing electronic file when originally transmitted was reduced to text at my direction; that said transcript is a true record of the proceedings therein referenced; that I am neither counsel for, related to, nor employed by any of the parties to the action in which these proceedings were taken; and, furthermore, that I am neither a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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