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21ST CENTURY CURES: MODERNIZING CLINICAL TRIALS

WEDNESDAY, JULY 9, 2014

House of Representatives,

Subcommittee on Health,

Committee on Energy and Commerce,

Washington, D.C.

The subcommittee met, pursuant to call, at 10:02 a.m., in Room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts [chairman of the subcommittee] presiding.

Present: Representatives Pitts, Burgess, Whitfield, Shimkus, Murphy, Blackburn, Gingrey, McMorris Rodgers, Lance, Cassidy, Guthrie, Griffith, Bilirakis, Ellmers, Barton, Upton (ex officio), Pallone, Capps, Green, Barrow, Castor, and Waxman (ex officio).

Staff Present: Clay Alspach, Counsel, Health; Gary Andres, Staff Director; Matt Bravo, Professional Staff Member; Leighton Brown,

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Press Assistant; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Oversight; Ziky Ablya, Minority Staff Assistant; Eric Flamm, Minority FDA Detailee; Debbie Letter, Minority Staff Assistant; Karen Lightfoot, Minority Communications Director and Senior Policy Advisor; Rachel Sher, Minority Senior Counsel; and Matt Siegler, Minority Counsel.

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Mr. Pitts. Subcommittee will come to order.

Chair will recognize himself for an opening statement.

Part of the work of our 21st Century Cures Initiative is to identify existing roadblocks to speeding treatments and cures to patients. One of these barriers is the current clinical trial process. Among the regulatory and administrative burdens associated with clinical trials are the expanding cost and size. While it takes on average approximately 14 years and $2 billion to bring a new drug to the market, a large portion of that cost is spent in recruiting and retaining subjects for clinical trials. It is often difficult to identify potential participants due to a shortage of centralized registries, low awareness of the opportunity to participate in clinical trials, low patient retention, and lack of engagement among community doctors and volunteers.

Widespread duplication of effort and cost also occurs because research is fragmented across hundreds of clinical research organizations, sites, and trials, and information regarding both the successes and failures of clinical trials is rarely shared among researchers.

Finally, in many cases, researchers have been slow to utilize technology such as electronic health records and Web-based platforms in their trials, which is also a barrier to greater collaboration and information sharing. This expensive and antiquated clinical trials

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model is simply not acceptable in the 21 Century. We can and must do better because patients deserve better.

Researchers and physicians are going to have to strengthen the recruitment and retention of volunteers for their trials, adopt new technologies, and above all, collaborate to build efficient and effective clinical trials.

I would like to thank all of our witnesses for being here today. I look forward to hearing of their ideas. I yield the remainder of my time to Dr. Burgess, vice chairman of the subcommittee.

Dr. Burgess. Thank you, Mr. Chairman, for the time. And thanks to our panelists for being here this morning. Certainly look forward to a good and lively discussion.

In many ways, randomized clinical trial, this country has set the gold standard for clinical trials, the rigorous investigative approach that we require. It does not mean that you can't make changes nor that you should not make changes to keep up with emerging science and new techniques in investigational review all the while keeping a close and careful eye on patient safety. Failure to adapt could see what was once considered to be the standard of excellence in regulation quickly look out of place and out of touch with the field to which it applies.

Evidence A, Exhibit A is personalized medicine and the ability of the human genome to play a role in that. We are approaching a time when treatments could be tailored for a person's specific genetic code.

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There is no way such a revolutionary approach to treatment could be evaluated in the same way as a single-molecule drug meant for large populations.

Mr. Chairman, I certainly appreciate the subcommittee asking the question, how can we build in more flexibility? How can we stimulate innovation into the trial process so that these cures, which are just over the horizon, can become the reality of therapies for our patients?

These changes must ultimately retain the integrity needed to ensure that the end product is safe and effective. We cannot be caught off guard and risk watching innovative therapies suffocate at the hands of a regulatory system that has not kept up or further cripple the regulatory system by the approval of products that inherently are unsafe.

I welcome the testimony of our witnesses today. I will yield back to the chairman.

Mr. Pitts. Chair thanks the gentleman.

Now recognize the ranking member of the subcommittee, Mr. Pallone, 5 minutes for an opening statement.

Mr. Pallone. Thank you, Chairman Pitts. Today we continue our work on the 21st Century Cures Initiative, and the input from these hearings is valuable to our discussion. One of the primary lessons we have learned thus far, and I expect we will continue to hear today, is that discovering cures and effective treatments is complicated and

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difficult. But in the end when medical advances reach patients, we must ensure that they are safe and effective. And so I welcome today's discussion on clinical trials, which is a foundation of our drug and device regulatory system as well as the challenges and opportunities there are for modernization of the system.

Clinical trials give researchers, drug, and device developers and doctors a way to translate scientific advances into treatments for patients. While not every trial is a success, with every trial more knowledge is gained about drugs and devices that can be used to aid in the development of a future drug.

I think we would all agree that NIH and FDA are world leaders. They have proven that they have the ability and authority to integrate the newest science into their policies and approaches. The NIH-supported Human Genome Project has opened up a world of potential new drug treatment. The ground-breaking public-private collaboration of the Lung Cancer Master Protocol, or Lung-MAP, which we will hear about from our witnesses today, represents an innovative approach to clinical testing.

Meanwhile, just last year, three-quarters of the new drugs approved by FDA were approved in the U.S. before any other country.

But there is nothing wrong with always striving to be better. The clinical development phase is the longest and most expensive period of product development, so it is important that we explore new tools,

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standards, and approaches that can be taken to assess the performance of medical advances.

Throughout this initiative, the question remains how Congress can advance these goals. The effort is a worthy one. It has been a great way for members and the public to explore and understand the complexity of issues that goes into discovery, development, and delivery of medicine.

But I have to question my colleagues that when it comes to science, too much or too little is a hard balancing act especially to dictate in statute. We can't be the science experts. The greatest role Congress can play is ensuring that our Federal agencies have the flexibility and resources to apply the best regulatory science available.

On Friday, the subcommittee will hold another and related hearing on the engagement of the patient perspective during the development process. And I am glad that FDA will appear before this subcommittee then to talk about a number of innovative approaches they are taking in their recent regulation of drugs and devices.

I think that, Mr. Chairman, I think it is an exciting time in science and there are some amazing stories to be told. But despite this progress, there is more that can be done. But again, these are complicated issues that I hope we will continue to examine very carefully.

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I would like to yield my last 2 minutes to Congresswoman Capps.

Mrs. Capps. Thank you to my colleague for yielding me time, and I thank you, Chairman Pitts and Ranking Member Pallone, for holding this important hearing.

I appreciate that this subcommittee wants to take action on this issue. It is a large one. Questions: How do we design a more modern clinical trial? How do we include the right mix of participants so the data are meaningful? How do we ensure that the data analyses performed actually look at differences on gender and ethnicity? How could post-market surveillance and future passive data monitoring help inform our current system?

These are just a few of the many critical questions, and I encourage the subcommittee to have additional hearings so that we can truly focus on the many issues under the umbrella of modernizing clinical trials.

This is an issue very near and dear to me. For almost 10 years, I have worked to improve clinical trials and especially those involving women and children. And we have made some progress in recent years, and this has been with the passage of FDASIA and my own National Pediatric Research Network Act.

But, as you all know, there is much more work to do. And so I thank you all for being here. And I look forward to your testimony. And that is all I have to say on -- I could yield back to the ranking

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member or just -- or yield to any of my colleagues. I will yield back.

Mr. Pitts. Chair thanks the gentlelady. Now recognize the chairman of full committee, Mr. Upton, 5 minutes for an opening statement.

The Chairman. Thank you, Mr. Chairman. You know, at our first 21st Century Cures roundtable we learned that there are treatments for only about 500 of the more than 7,000 known diseases that affect our Nation's patients. We have also heard about the increasing time and expenses involved in bringing new drugs and devices to market, and we learned that the costs and regs surrounding clinical trials are a primary contributor to this delay. This means that new treatments and cures cost more and they are getting to patients more slowly. That system is simply unsustainable.

So here in the U.S., it is incredibly complicated to navigate the processes involved in simply getting a trial up and running. Particularly for small companies. Overall, the size, duration, costs, failure rates are higher than ever. In some cases, trials are being moved overseas as a direct result of those challenges. This leaves patients in the U.S. waiting longer for cures and treatments, and it also gives jobs -- takes those jobs away from folks here at home. Safety is always the top priority. And I know, I know that we can -- we can do better. We must work together to remove any needless administrative or operational burdens that do not benefit patients.

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In addition, we would like to learn more about recent advances in technology and data collection that can help modernize our system, encourage better participation, and certainly allow for continued learning about the risks and benefits of new drugs and devices in the real world.

How can we take what we learn in the development and delivery phases and translate that back to new, innovative discovery in this cycle of cures? How can we leverage patient registries in innovative new protocols, like the Lung-MAP trial, as well as other collaborative efforts into more advances into molecular medicine? Electronic health records, increased data sharing, and patient-reported outcomes will undoubtedly play a critical role in this regard. Ultimately, it is going to accelerate and modernize the discovery, development, and delivery cycle.

So today's hearing is yet another opportunity to discuss what can we do to further our journey on the path to cures.

And I would yield to Marsha Blackburn.

Mrs. Blackburn. Thank you, Mr. Chairman. And I want to welcome all of you. We appreciate that you are here as we look at modernizing clinical trials.

Federal law requires that medications proposed for human use be safe and efficacious. That means that our constituents can expect medicines to do exactly what they are advertised to do and that any

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side effects are going to be clear and apparent to these patients. And the major mechanism by which medicines are found to be safe and efficacious are the phase III clinical trials, which test the drugs against placebos and the other known treatments. We all appreciate that process. And what we want to do is look at how we are going to be able to modernize this process as we go through the trials with large groups of people, sometimes thousands, with the intent of finding the side effects that could harm even a small percentage of individuals.

The large groups also make the statistics work, giving greater assurance that the drug does do what it is purported to do. The importance of the phase III trials is reflected in the statutory language in the FD&C Act. The FDA generally requires drug companies to sponsor at least two such clinical trials for a new drug. I would be interested to hear from you: Do you think that is enough? Too much? How should that be changed? Also, the phase III trials are the gold standard for drug approval. They have their limitations. How would you address those limitations? Today we are going to look at that gold standard and the limitations of the phase III trials. And hear of your base to build upon what we have learned in order to speed safe and efficacious treatments to patients.

I thank you for your time, and I yield back to the chairman.

The Chairman. Yield back.

Mr. Pitts. Chair thanks the gentlelady.

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Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for an opening statement.

Mr. Waxman. Thank you, Mr. Chairman.

The topic of this hearing is an important one. Clinical trials are the bedrock of modern medical product development. We rely on clinical trials to demonstrate that our drugs and devices are safe and effective, and we rely on the willingness of people to volunteer to participate in these trials. So of course, we want to ensure that clinical trials are conducted using the most modern tools and technology that science has to offer.

We also need to ensure that clinical trials are conducted in the most efficient manner possible. That is why NIH and FDA have been leaders in working with academia and industry to identify areas in which the clinical trial process can be improved. These improvements could include encouraging the use of centralized institutional review boards, developing standards for harmonizing the collection and exchange of data, and maintenance of patient registries to facilitate the recruitment of patients for clinical trials. And I look forward to hearing more today about such efforts.

How Congress can help advance these goals is a complicated question. The 21st Century Cures Initiative is useful because it is shining a light on some important issues surrounding how drugs and devices are developed and ultimately delivered to patients.

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There are some clear areas where Congress could legislate. We should ensure that both FDA and NIH have the resources they need to remain the gold standard in observing clinical trials. But when it come to legislating how clinical trials are conducted, we need to proceed with great caution. Congress should not be in the business of dictating the kind or level of evidence needed to permit drugs and devices to go on to the market. That decision is solely the task of the scientific experts at the Food and Drug Administration. We should not force FDA to prematurely accept novel technologies. Our job should be to ensure that FDA has the regulatory authority needed to make use of the latest scientific advances.

When FDA testifies on Friday, the agency can tell us about how it is applying novel proceedings to clinical trials in their regulation of drugs and devices. I would also like to know whether the agency believes it has the authority necessary to adopt new approaches and whether other new statutory powers are necessary. In this area, we need to be careful not to try to fix things that are not broken. That could harm a system that is already working. We should create policies that foster scientific advances. But we should not enact regulatory policies based on how far we wish scientific development has progressed.

I thank you, Mr. Chairman. And I am willing to yield my time to anyone who might want it. Otherwise, I yield it back.

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Mr. Pitts. Chair thanks the gentleman. That concludes the opening oral statements of the members. All members' written open statements, opening statements will be made a part of the record.

We have one panel today with seven witnesses. And I will introduce them in the order that they present their testimony.

First, Dr. Robert Meyer, Director, Virginia Center for Translational and Regulatory Sciences, University of Virginia School of Medicine; Dr. Aaron Kesselheim, Assistant Professor of Medicine, Harvard Medical School, Director, Program on Regulation, Therapeutics, and Law Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital; Mr. Bill Murray, President and CEO, Medical Device Innovation Consortium; Dr. Jay Siegel, Chief Biotechnology Office and Head Scientific Strategy and Policy, Johnson & Johnson; Dr. Roy Herbst, Chief of Medical Oncology, Yale Cancer Center; Dr. Sundeep Khosla, Director, Center for Clinical Translational Science, Mayo Clinic; and Ms. Paula Brown Stafford, President, Clinical Development, Quintiles.

Thank you for coming. You will each have 5 minutes to summarize your testimony. And your written testimony will be placed in the record.

Dr. Meyer, we will start with you. You are recognized for 5 minutes for opening statement.

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STATEMENTS OF ROBERT J. MEYER, M.D., DIRECTOR, VIRGINIA CENTER FOR TRANSLATIONAL AND REGULATORY SCIENCES (VCTRS), UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE; AARON S. KESSELHEIM, M.D., J.D., M.P.H., ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, DIRECTOR, PROGRAM ON REGULATION, THERAPEUTICS, AND LAW (PORTAL DIVISION OF PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS, BRIGHAM AND WOMEN'S HOSPITAL; WILLIAM V. MURRAY, PRESIDENT AND CEO, MEDICAL DEVICE INNOVATION CONSORTIUM; JAY P. SIEGEL, M.D., CHIEF BIOTECHNOLOGY OFFICE AND HEAD, SCIENTIFIC STRATEGY AND POLICY, JOHNSON & JOHNSON; ROY S. HERBST, M.D., PH.D, CHIEF OF MEDICAL ONCOLOGY, YALE CANCER CENTER; SUNDEEP KHOSLA, M.D., DIRECTOR, CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE, MAYO CLINIC; AND PAULA BROWN STAFFORD, MPH, PRESIDENT, CLINICAL DEVELOPMENT, QUINTILES

STATEMENT OF ROBERT J. MEYER, M.D.

Dr. Meyer. Thank you, Chairman Pitts, Ranking Member Pallone, and members of the committee.

As stated, I am Dr. Bob Meyer, where I direct the -- and I direct the Center for Translational and Regulatory Sciences at the University of Virginia. I am, by background, a pulmonary physician, and previously held senior leadership roles within the Center For Drug

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Evaluation and Research at FDA as well as in Merck Research Labs, where I headed global regulatory strategy, policy, and drug safety, and was a key participant in their late-staged development committee, which the committee that was responsible for the oversight of late-stage development trials within Merck's portfolio.

While I am now academics, I think I have a very real and tangible experience with regard to clinical trials challenges from both a regulatory and industry perspective, and, therefore, I am pleased to be here today.

Modern clinical development programs are large, complex, and usually global in scope and in conduct. And are increasingly expensive to conduct.

Compounding this rising cost is the fact that the success rate for drugs entering into phase III to achieve final regulatory approval is falling, and the rate is now approximating only 50 percent.

There are myriad of drivers that have contributed to the growth and larger, longer, and more complex phase III trials, including regulatory demands. However, I think it is important to focus beyond FDA in the considerations on how to address some of these issues. And let me speak to a few of these. I would say that I am going to keep this statement short because I believe many of these points will be more eloquently made by others on the panel.

The first consideration that I would raise is better trial

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standardization. In phase III programs, there is a large amount of time expended getting from study concept to the first patient enrolled. And the sponsors usually recapitulate these efforts for each program as if each one is a wholly new effort. This then raises two important points for consideration.

First is the enhanced development of effective, lasting, durable clinical trials networks. Networks can bring efficiencies such as having identified patient populations and qualified and ready clinical sites that can reduce some of the time and effort spent in study startups. There are efforts towards clinical trial network development in certain disease areas, such as the National Cancer Trials Network. However, this model is not as widespread as it should be or could be, particularly taking into account the varied areas of unmet medical needs.

Second concept is the development of master protocols. Such master protocols could serve as the basis for use by different investigators or sponsors with minimal modification, save for the details of the particular test product.

An added benefit of wider use of shared standardized protocols is this would also enhance the ability to interpret these trials in cross-study comparisons to assess relative efficacy, safety, or other attributes considered important to physicians, patients, and payers, since the patient populations and end points would be highly similar.

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Another consideration is the increasing complexity and design of modern clinical trials. This trend to increasing complexity is reflective of the fact that modern trials are designed to address an increasing number of demands from differing regulatory demands across the globe, differing payer expectations, differing market claims sought, the use of new exploratory science or end points within the trials, and interest and input of key opinion leaders who participate in the design of the trials.

I believe sponsors could benefit from further concerted efforts to simplify trials by using multidisciplinary groups within the company and outside the companies tasked to maximize the value of the trial while minimizing the complexity and cost.

I also believe FDA could aid in this effort in the end of phase II advice. But to do so they would need to recruit more experienced industry personnel with practical clinical trial design in the operations experience because this kind of expertise is rare within the agency.

An additional consideration in reducing clinical trial expenditures is moving further away from the paradigm of face-to-face clinical evaluations as the gold standard for patient evaluation. There is an increasingly sophisticated ability to assess patient status and accrue sophisticated clinical data via new technologies.

So in light of the other expertise on the panel, let me close by

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saying these efforts to think about how we can modernize clinical trials are critically important. However, I think that the evaluation of safety and efficacy is a critical safeguard to patients within the U.S. And I think the way that this currently is done within the U.S. is, in fact, the gold standard not only within the U.S. but across the globe. And I would urge that the increasing daunting costs and the challenges of medical clinical trials are addressed in a way that preserves the assurance that drugs on the market are safe and effective.

We must seek a way to deploy practice, into practice the efficient modern clinical trials, incorporate new technologies and science where appropriate and validated while maintaining the integrity of the regulatory progress.

Thank you for this opportunity to participate in the hearing.

Mr. Pitts. Chair thanks the gentleman.

[The prepared statement of Dr. Meyer follows:]

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Mr. Pitts. Now recognizes Dr. Kesselheim for 5 minutes for an opening statement.

STATEMENT OF AARON S. KESSELHEIM, M.D.

Dr. Kesselheim. Thanks very much, Subcommittee Chairman Pitts, Ranking Member Pallone, and members. I am Aaron Kesselheim. I am a physician, lawyer, and health policy researcher at Harvard Medical School. And it is an honor to have the opportunity to share my thoughts with you about modernizing clinical trials and helping expedite access to new prescription drugs and medical devices.

About 50 years ago, Congress decided that new therapeutics should have their efficacy and safety demonstrated before they could be widely used by patients. This wasn't a capricious attempt by legislators to prevent patients from getting the treatments they need, but a rational response by public servants to major public health tragedies caused by the lack of such proof.

When Congress originally gave FDA this power, it did not require any particular kind of test. All that is statutorily required is that manufacturers provide substantial evidence that the drug will have the effect it purports to have, with "substantial evidence" being defined as adequate and well controlled investigation.

Unfortunately, some manufacturers will not subject their

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healthcare products to studies meeting even these minimal criteria without the FDA standard-setting authority. Take a look at the dietary supplement market if you don't believe me. Indeed, in the decade after these regulations were put in place, FDA regulators removed hundreds of drugs that failed to show sufficient evidence of effectiveness upon clinical study.

To meet these criteria, the FDA prefers randomized trials with blinded assignment and placebo or active comparator controls. And so does the world scientific community. Is worth recalling that a randomized control trial was once an innovation. The basic requirements for conducting these trials became recognized and codified slowly over the course of the 20th century after decades of debate and consideration, leading to consensus about their most important characteristics.

At the same time, subjecting a new product to a formal, randomized control trial or testing a hard clinical end point could delay availability of promising products to some patients in life-threatening circumstances. Fortunately, as currently written, the law gives the FDA flexibility to adapt -- to accept data short of traditional randomized trials to approve therapeutics for important unmet needs or where randomization may be ethically or practically impossible.

These products may get assigned by the FDA to special fast track,

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or accelerated approval pathways, or receive Congressionally-authorized designations that signal their special status, like "orphan drug" or "breakthrough drug" or "humanitarian device."

Studies conducted by myself and others show that products with these designations are often provided with expedited review by the FDA, many receiving approval based on uncontrolled studies and small populations.

Expedited approval pathways and special designations are common at the FDA. In 2012, 26 of the 39 new drugs approved qualified for at least one such program. And the FDA now approves about two-thirds of new drugs earlier than its counterparts in Europe.

When medical products are approved without being subject to randomized trials testing real clinical endpoints, it puts patient at increase risk. Medical history is littered with drugs and devices approved on the basis of unvalidated biomarkers that have their indications later withdrawn or altered, or cancer drugs, originally approved on uncontrolled trial later demonstrated in better controlled trials finally conducted a decade later to actually increase the risk of death.

In 2012, the multi-drug resistant tuberculosis drug, bedaquiline, was approved on the basis of two short-term trials testing about 200 patients after being granted accelerated approval status,

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fast track, orphan drug status, and priority review. In these studies, the drug was only shown to improve the questionable surrogate endpoint of converting sputum from tuberculosis positive to negative. But two-and-a-half times as many patients died from tuberculosis in the bedaquiline group than the control group. Patients with tuberculosis want to be cured, they don't want to die with cleaner sputum.

How do patients and individual physicians now make sound benefit/risk determinations about this drug or others like it in the absence of more conclusive scientific data?

The prospect of approving more drugs on the basis of trial designs that diverge from traditional randomized trials also puts pressure on the timely conduct of confirmatory clinical trials and post-approval surveillance systems. But studies show that manufacturers' commitments to continue studying their products after approval may be delayed or incomplete.

Once a drug is FDA approved for a certain indication, convincing patients to subject themselves to further randomized trials of the drug for that indication can be challenging because patients can receive the drug outside the trial. It is no wonder that the FDA gave the makers of bedaquiline until 2022 to complete confirmatory trials of that drug's effectiveness in tuberculosis.

In summary, the prospect that researchers can design new ways of conducting clinical trials of investigational drugs is exciting. And

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I hope that the best of these truncated designs are proven to provide the same level of confidence as standard randomized controlled trials.

But the FDA already has the flexibility in its laws and regulations to accept innovative study designs short of randomized trials and validated biomarkers that can accelerate the testing of truly important new drugs and medical devices.

The fast track process reduced clinical development time of a new drug from 8.9 to 6.2 years; accelerated approval drugs have an average of just 4.2 years of development.

And the FDA already exercises its flexibility to a remarkable extent. If regulators and others in the medical community are still skeptical about certain biomarkers and clinical trial designs, it is probably because the science supporting them is still in its infancy; in which case, forcing approval of the drugs or devices to which they are applied would be dangerous and counterproductive for the very patients we are all trying to help. Thank you.

Mr. Pitts. Chair thanks the gentleman.

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[The prepared statement of Dr. Kesselheim follows:]

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Mr. Pitts. Chair now recognizes Mr. Murray, 5 minutes for an opening statement.

STATEMENT OF WILLIAM V. MURRAY

Mr. Murray. Chairman Pitts, Ranking Member Pallone, and subcommittee members, thank you for the opportunity to testify. My name is Bill Murray, and I am president and CEO of the Medical Device Innovation Consortium. During my 25 years in this industry, I have had the opportunity to lead multi-billion dollar global businesses as well as two early stage companies. These innovative businesses were founded on technology developed in the United States. In recent years, however, these businesses have faced a more difficult regulatory and reimbursement environment in the United States which is challenging our country's position as a global leader in medical device innovation.

I applaud the committee's bipartisan leadership in initiating the 21st Century Cures Call to Action and its commitment for finding solutions to help the U.S. healthcare industry maintain global leadership.

MDIC is a public-private partnership between government agencies including FDA, CMS, and NIH, non-profits, and industry. MDIC is focused on the medical device ecosystem. We collaborate on advancing regulatory science, by which I mean the tools, standards, and

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approaches that regulators and innovators use in the development and review of medical devices. We believe that improving regulatory science will offer concrete ways to make patient access to new medical technologies faster, safer, and more cost effective.

Clinical trials are amongst the biggest challenges. The time, complexity, and cost of conducting clinical trials, along with the uncertainty of outcomes, makes them a challenge for both regulators and innovators. And based on a survey of over 200 medical device technology companies, it takes an average of 6-1/2 years and $36 million before a new class 3 device even reaches the pivotal study.

We need new approaches if we are to continue fostering innovation. MDIC's goal is to improve the safety and effectiveness of products being introduced to the market, reduce clinical trial timelines and costs, and give U.S. patients earlier access to beneficial technologies.

MDIC's work includes several high priority initiatives. First, MDIC is working to improve the design of clinical trials. Medical device clinical trials are increasingly complicated. MDIC is examining current trial designs to better understand how much of the collected data are used and the ways in which clinical trials may be unnecessarily complex. We are exploring possible alternative trial designs that still supply high quality data on the safety and effectiveness of medical devices.

MDIC is also supportive of FDA Center for Devices and Radiological

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Health, efforts to balance pre- and post-market data requirements. Providing the reasonable threshold for clinical data during the pre-market process while continuing to collect data in the post-market setting is a win for patients and innovators.

Second, MDIC is investigating ways to reduce the barriers to conducting early feasibility studies in the United States. These first in human studies are a critical step in the approval process of many new medical devices. But increasingly, they are performed outside the United States. The reasons for this include economic incentives offered by other countries for companies to invest abroad, but they also include concerns the regulatory approval process is slower, less predictable, and less flexible than the United States. As a result, U.S. patients often have to wait longer for access to new medical devices.

CDRH recognizes this issue and has taken initial steps to address it through a new policy in 2012. MDIC is building on that work by exploring new methods and tools that support early feasibility studies, such as incorporating validated computational modeling and simulation data into the assessment process. We feel strongly that American patients should be the first to benefit from cutting-edge American technologies.

Third, MDIC is conducting research to better understand the data on patient preferences about the benefits and risks of medical devices.

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Supported by funding from FDA, MDIC is developing a catalog of scientifically valid ways to measure patient perspectives, and we are developing a framework that can support the use of the data in the regulatory process.

Fourth, MDIC is convening experts to help the medical device industry harness the power of computational modeling and simulation. Currently, medical devices lag behind such fields as aerospace and automotive in the use of modeling and simulation tools. The development and use of regulatory-grade tools has the potential to revolutionize the field, enabling developers to generate more ground-breaking ideas, test them with greater confidence, and bring them to patient more safely and quickly, while reducing the costs of clinical trials. Moreover, modeling and simulation may soon play a larger role in the treatment planning and the realization of personalized medicine in the clinic.

MDIC is making progress on these important initiatives, but more needs to be done. We encourage Congress to support efforts to strengthen regulatory science and facilitate public-private partnership collaborations to improve the innovation environment in the United States.

Thank you again for the opportunity to testify about MDIC's collaborative efforts to support medical device innovation that will benefit patients. I will be happy to answer any questions.

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Mr. Pitts. Chair thanks the gentleman.

[The prepared statement of Mr. Murray follows:]

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Mr. Pitts. And now recognize Dr. Siegel, 5 minutes for an opening statement.

STATEMENT OF JAY P. SIEGEL, M.D.

Dr. Siegel. Thank you, Chairman Pitts and Ranking Member Pallone and members of the committee.

I have been working on clinic trial improvements for over 30 years from the diverse perspective of a senior U.S. --

Mr. Pitts. Is your mic on? Thank you.

Dr. Siegel. I have been working on clinical trial improvements for over 30 years, from the diverse perspectives of a senior USFDA official, an industry R&D leader at Johnson & Johnson, and a participant in many broad collaborations, including the International Collaboration for Harmonization, the Society For Clinical Trials, and the Clinical Trials Transformation Initiative.

I applaud and thank the committee for the 21st Century Cures Initiative and today's focus on clinical trials modernization.

Our clinical research enterprise is critically important for medical progress, but was largely designed for conditions that prevailed years or decades ago. We have before us new tools and opportunities to modernize it and thereby to usher in a new era of efficient translation of scientific advances and to medical advances

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in 21st century cures.

I will briefly discuss four of these opportunities: Use of electronic health records, use of biomarkers, creation and use of clinical trial networks and consortia, and engaging patients as collaborators in the research process.

The adoption of electronic health records provides the potential to collect data efficiently in the settings in which health care is being delivered, creating a learning healthcare system. Large scale registries of patients with a shared condition can be constructed, allowing studies of disease course, risk factors, biomarkers, and treatment effects. The powerful tool of randomization could be applied to such cohorts, creating large simple clinical trials in the care setting. The resultant enhancement of the ability to learn about the effects of medicinal products while in clinical use could allow earlier availability of important new therapies with assurance that additional information would be collected reliably and efficiently after approval.

Full realization of the promise that electronic health record enhanced research holds will require addressing several needs, including standardization, interoperability, and data quality of the systems; research into how best to compile and use the data; and reassessment of the regulatory frameworks that protect patients.

The rapidly increasing ability to collect and analyze genomic,

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proteomic imaging and other information allow incorporating that information into clinical trials as biomarkers. One valuable use of biomarkers in clinical trials is as surrogate end points, which, if reasonably likely to predict clinical benefit, can support the accelerated approval of new therapies. The success of accelerated approvals in bringing important new drugs to patients in need sooner, together with the ability to measure many new biomarkers, suggests that wider usage of biomarkers for accelerated approval would be beneficial. In the FDA Safety and Innovation Act of 2012, Congress encouraged such wider usage.

Use of biomarkers for patient subgrouping and response monitoring can crucially enhance several other aspects of clinical research, including personalized medicine research, disease prevention research, and adaptive clinical trials. Government, in partnership with academia, patient groups, and industry, can create and operate clinical trial networks that provide a rapid and efficient means for assessing promising new therapies.

Networks have already led to substantial advances in clinical research, and there is potential to address more disease, to create broad consortia, and to utilize powerful new tools, such as electronic health record-based trials and ongoing biomarker-driven adaptive design trials, such as Lung-MAP.

Patients bring to clinical research valuable perspectives and

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insights and often strong motivation to contribute. Enhanced participation of patients in the design and conduct of clinical trials can be expected to improve many aspects of trials. Patient-reported outcomes together with patient-informed risk/benefit assessments should play a larger role in clinical trials and product development.

Additionally, efforts to involve more patients in clinical research will help unleash the power of a learning healthcare system while helping ensure that our medical knowledge is derived from the experience of a more diverse and representative population.

Mr. Chairman, I thank you and the committee for your invitation and your attention.

Mr. Pitts. Chair thanks the gentleman.

[The prepared statement of Dr. Siegel follows:]

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Mr. Pitts. Now recognize Dr. Herbst, 5 minutes for opening statement.

STATEMENT OF ROY HERBST, M.D.

Dr. Herbst. Good morning, Chairman Upton, Ranking Member Waxman, Subcommittee Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. Thank you for inviting me today to share my experience regarding innovative clinical trials for cancer patients. I am Dr. Roy Herbst, and in my role as chief of oncology at Yale, I care for patients with lung cancer, conduct and collaborate on basic research, and work on clinical trials from phase I, first in human, to phase III. Over the last 2 years, I have been working with the Friends of Cancer Research, which was founded and is led by Ellen Siegel, the National Cancer Institute, SWOG, a cancer cooperative group, and the FDA on an innovative public-private partnership approach to clinical trials. And I am honored to be invited to participate in this important hearing today.

Cancer is the second most common cause of death in the United States, with over half a million Americans expected to die of this disease in 2014. Cancer is a disease that is accompanied by much pain and suffering, loss of life and productivity. Despite advancements in surgery and drug therapy, many cancers remain incurable. Lung

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cancer, the number one cause of cancer death, is one such disease. And, as a specialist in this area, I often see patients with advanced disease who have very limited treatment options. For this reason, together with my colleagues in the field, we strive to develop new therapies for these patients so that we may provide them with a cure or at least with more quality of life and time with their families. I am working hard to personalize care; I want to match a patient's tumor profile with a best treatment, with the overarching goal to find ways to provide more active, less toxic, and more cost-effective therapies.

I am happy to say we are making progress. Due to the country's investment in research, in 2014, we can now sequence every gene in a tumor, including the 25,000 protein-coating genes. This is amazing technology and science. However, it remains limited. Why? Because, one, it is still only available to a minority of patients; two, it is expensive and often not covered by insurance; three, the informatics and data-interpretation challenges are overwhelming; and, most importantly, we have still do not know how to translate this information into therapeutic benefit.

Hence, clinical trials are essential for this process and the need to modernize for the molecular age is very important. Often clinical trials are limited by numerous challenges, including the startup time, accrual expense, and the need to identify and define subpopulations of patients that makes trial enrollment difficult.

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Developing a potential therapy from the initial discovery stage through clinical testing and regulatory approval is a complicated, expensive, and often inefficient process that can take up to 15 years.

Let me give you an example. In recent years, we tried to study a drug that affects 10 percent of patients with lung cancer. That meant we had to screen 100 patients at Yale to find 10; only six of those patients were then eligible with good enough status to go on the trial; we treated two. That is totally unacceptable, it is not good for the patients, it is not good for the clinical trial, it is not going to advance our cause.

With this in mind, the Lung Cancer Master Protocol, known as Lung-MAP, is an innovative, groundbreaking clinical trial designed to facilitate efficiencies and advance the development of targeted therapies for squamous cell lung cancer of the lung, one of the worst types of this cancer. The concept of a lung map was developed at the 2012 Friends of Cancer Research Brookings conference on clinical cancer research, and at the same time, by the National Cancer Institute Lung Cancer Steering Committee.

Since the release of that initial concept paper through the intense collaboration of many, Lung-MAP was initiated and opened in a very rapid year and a half. The goal is to develop a biologically-driven approach, building on the NCI-funded Cancer Genome Atlas, TCGA, to identify targets.

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In Lung-MAP, a master protocol will govern how multiple drugs, each targeting a different biomarker, will be tested as potential treatments for lung cancer. Each arm of the study will test a different drug that has been determined to target a unique genetic alteration. The use of cutting-edge screening technology will help identify which patient is a molecular match to each arm. This will create a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs. We want to get the right drug to the right patient at the right time. This is good for patients because it allows them, with as many as 500 sites to be opened around the U.S., to have access to the drugs and allows us to study effects so eventually they can become approved and be available to even more people around the world.

One of the benefits of the Lung-MAP, enrollment efficiency. Grouping these studies under a single trial reduces the overall screen failure that is great for patients. Operational efficiency, a single master protocol can be amended as needed as drugs enter and exit the study without having to stop and restart; cost efficiency, as a result of shared services, utilization of existing infrastructure and avoiding redundancy, this public-private partnership will operate at cost substantially less than individual trials.

This consistency among trials, predictability on the outcome, full transparency with an oversight committee and a drug selection

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committee benefit to patients, and seamless movement from phase I to II trial design. In fact, the FDA was very closely involved with the idea for this whole concept.

My time is running short. But I will tell you that I hope this committee can help us and with the issue of biomarkers, how to develop better biomarkers for these trials, how to regulate the diagnostics for these trials. Certainly the public-private partnership that we have developed is one that needs to be enhanced and helped and incentivized.

And, of course, finally resources. We have been working with the NCI. And the budget is flat at best. And certainly we want to bring more of those drugs to patients.

So as I conclude, Lung-MAP is a public-private partnership where each sector has committed to do business differently. Together we believe that Lung-MAP can demonstrate a new model for high quality drug development in less time at less cost for more people, and most importantly, improve the lives of patients with lung cancer. I am happy to report the first patient on the study enrolled at Yale yesterday. The shared goal of accelerating the pace in which new drugs are developing is a driving force behind this partnership. We know that this committee shares that goal, and so we thank you for taking on this important 21th Century Cures Initiative. Thank you.

Mr. Pitts. Chair thanks the gentleman.

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[The prepared statement of Dr. Herbst follows:]

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Mr. Pitts. And now recognize Dr. Khosla, 5 minutes for an opening statement.

STATEMENT OF SUNDEEP KHOSLA, M.D.

Dr. Khosla. Good morning. My name is Sundeep Khosla. I am a practicing endocrinologist and dean For Clinical and Translational Science at Mayo Clinic in Rochester, Minnesota. I am also the principal investigator at the Mayo Clinic Clinical and Translational Science Award, or CTSA, from the National Center For Advancing Translational Sciences, NCATS, at NIH. I salute the 21st Century Cures Initiative, and am please to share some thoughts on the opportunities and challenges we face in bringing new treatments to patients.

Mayo Clinic has facilities in six States and provides care for more than 1 million people annually from all 50 States and 135 countries around the globe. In addition to clinical care, Mayo has a robust research program, including clinical trials. Over the years, Mayo has conducted pivotal clinical trials in many areas, including diabetes, osteoporosis, heart disease, and cancer. Mayo Clinic won a Nobel Prize in Physiology and Medicine in 1950 for the discovery of cortisone and its clinical applications. Conducting clinical trials is an extremely high priority for Mayo.

With the Congressional investment in NIH over the past several

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decades and the NIH-supported human genome project, we are now in a truly exciting era where there are more possibilities for understanding diseases and developing new drugs and new treatments than ever before.

With these opportunities, however, have come significant challenges. To address these challenges, NIH Director Collins created NCATS in December 2011 to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementations of interventions that tangibly improve human health across a wide range of human diseases and conditions.

As astutely recognized by this committee, the clinical trials process needs modernization. NCATS is seeking to do just that by funding CTSAs at 62 sites around the country, thus essentially creating a network of potential clinical trial sites. The vision is that high priority clinical trials funded either by NIH or by industry could be run very efficiently through all or part of the 62-site network.

While implementation is not easy, there are three changes that would facilitate the work of the NCATS clinical trials network. One is institutional review board, or IRB reciprocity, between as many of the sites as possible. Because each institution has its own IRB, there are frequent and often lengthy delays in multi-center clinical trials as each IRB reviews and eventually approves a clinical trial protocol.

Reciprocity between as many sites as possible would mean that once the IRB at the primary site approved the protocol, that approval would

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be accepted by the remaining sites.

Second, there needs to be much greater interoperability of electronic health records. This could allow, for example, study investigators to rapidly search for study participants across all 62 CTSA sites.

Third, for a national network of clinical trial sites to truly function efficiently, there needs to be greater harmonization of regulations. For example, an investigator today must contend with different regulatory requirements from the Office for Human Research Protections, the FDA, and the Office for Civil Rights, all within HHS. Further complexity is added by State laws that may go beyond the Federal requirements.

What can Congress do to help facilitate clinical trials at the national level? I have four suggestions:

First, continue to support the efforts of NCATS and the CTSAs through ongoing and, if possible, enhanced funding.

Second, help develop policies that encourage IRBs to have greater reciprocity with other institutions.

Third, urge HHS to accelerate progress towards interoperability of electronic health records.

Finally, develop policies for greater harmonization of regulations across Federal agencies and across States.

Responsibility for modernizing clinical trials falls also on the

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shoulders of individual academic medical centers. Here are three ideas academic medical centers could consider to modernize clinical trials:

One, work to shorten the time required for study initiation through more streamlined contract negotiation with industry and for IRB approval.

Two, because disagreements over the use of biospecimens often cause considerable clinical trial delay, work to develop a simplified biospecimens policy that is broadly accepted across sites and companies.

Third, develop better electronic capabilities to enhance recruitment, screening, enrollment, and tracking of study participants.

In summary, the opportunities for bringing new treatments to patients have never been greater, yet significant challenges remain. Congress can help this effort by supporting discovery science, NCATS, and the CTSA system, and by removing roadblocks in the clinical trials process. Together government, the private sector, and academic medical centers must all step up and do all we can to rapidly deliver discoveries to the people who need them.

Thank you for your opportunity to testify today.

Mr. Pitts. Chair thanks the gentleman.

[The prepared statement of Dr. Khosla follows:]

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Mr. Pitts. And now recognize Ms. Stafford, 5 minutes for an opening statement.

STATEMENT OF PAULA BROWN STAFFORD

Ms. Stafford. Good morning, Chairman Pitts, Ranking Member Pallone.

Mr. Pitts. Make sure your button is pressed. Thank you.

Ms. Stafford. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the Health Subcommittee. Thank you for the opportunity to appear before you today. My name is Paula Brown Stafford. I am president of Clinical Development at Quintiles, the world's largest provider of biopharmaceutical development and commercialization services. We have more than 29,000 employees globally, including nearly 10,000 here in the U.S. We are engaged every day in helping bring better medicines to patients faster.

To give you a sense of our scope, over the past 10 years, we have enrolled nearly 1 million patients in clinical trials at over 100,000 investigative sites like Yale, Mayo Clinic.

Our experience and our role as a facilitator of the process gives us a unique vantage point on where the challenges and opportunities are in the drug development process.

We all agree the development process is too expensive, in excess

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of a billion per NME, and takes too long. Generally, that is 7 to 10 years. And, yes, patients are waiting.

Modernizing clinical trials is critical if we are to meet the goals we share of delivering medicines faster at less cost to patients who need them.

Quintiles works closely with our biopharma customers and the FDA to find better ways to design and execute studies to meet this goal, and we have had many collaborative successes to date, yet there is more to be done.

My remarks will focus on three areas for further innovation and a number of recommendations where Congress can help accelerate meaningful improvements.

First, with nearly 80 percent of total drug development time and cost spent on clinical trials, we must focus on patients, creating better ways to find the right patients for the right clinical trials. The bulk of time to conduct a clinical trial is spent in finding patients that meet the increasingly complex inclusion/exclusion criteria of trials today. Improving data collection and accessibility would facilitate more rapid identification of patients suitable for clinical trials. Without new approaches and better access to data, patient recruitment will become increasingly difficult, especially as we work to develop cures that are more targeted or personalized based on genomics.

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Second, there is much more room for improving the process of conducting clinical trials, reducing the timeline for each trial by eliminating redundancies and inefficiencies, particularly in what is known as the startup phase, where it can take up to 18 months just to get to a point where a study is open for patient enrollment.

Also standardization of clinical trials. The protocols, the data collection requirements would help to reduce repetitive activities that happen across trials.

Among private sectors, the Clinical Data Interchange Standards Consortium, CDISC group I chaired from 2012 to 2011, has recently even created data standards for a number of therapeutic areas, including multiple sclerosis, Alzheimer's, and asthma.

The third area is pathways. Alternative development pathways could speed the introduction of new therapies to address serious unmet medical needs as an alternative to the traditional three-phase clinical trial paradigm. Great strides have been made by the passage of FDASIA -- the anniversary is today, 2 years ago today. Also the creation of the breakthrough therapy designation and other expedited drug approval pathways. However, these have largely addressed FDA review time, which was 10 months, but not the much longer development time, which is 10 years.

So how can Congress help? A number of recommendations.

One, Congress could encourage the FDA to set goals for more

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frequent use of master protocols and adaptive designs. Both of these approaches allow multiple drugs to be evaluated in the same trial, identify affected and non-affected populations faster. And Quintiles has recently submitted a proposed master protocol for diabetes, CVOT, to the FDA, and are expecting comments later this month.

Congress could take steps to improve the quality and accessibility of the data to researchers and thereby improve the speed and accuracy of identifying the right patients for the right trial. Among these steps are incremental improvements to linkages between EHR and clinical research databases, better interoperability among EHRs, and examining where there are misinterpretations of HIPAA and other data privacy regulations that may be inadvertently hampering the use of de-identified data to improve research.

Congress should explore ways that the FDA and the NIH could encourage the use of central IRBs, which, in our experience, can cut the time to even start an individual investigative site for more than 100 to 45 days.

And Congress could encourage FDA to pilot alternative development pathways, similar to the adaptive licensing approach that the EMA is now piloting. The tools and science are in place to support alternatives whereby treatments could be tested and approved for limited use while ongoing studies would still be required.

Chairman Pitts, members of the subcommittee, I ask you and your

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colleagues to support these recommendations because at the end of the day a spouse, family member, a friend, or even you may benefit from the next drug discovery that a modernized clinical trial system brings forth.

Thank you.

Mr. Pitts. Chair thanks the gentlelady.

[The prepared statement of Ms. Stafford follows:]

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Mr. Pitts. And thanks all the witnesses for very thoughtful testimony. And we will begin questions and answers.

At this point, let me ask you for unanimous consent request to submit for today's hearing record four items. Letters to the editor of the New England Journal for Medicine questioning a number of assertions made in an article Dr. Kesselheim and others had published in the same publication on March 27. And these letters include a letter from Mark McClellan of the Brookings Institution and Ellen Siegel of the Friends of Cancer Research, a letter from the Infectious Diseases Society of America, and a letter from the Leukemia and Lymphoma Society.

Without objection, so ordered.

[The letters follow:]

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Mr. Pitts. I will now begin the questioning and recognize myself, 5 minutes for that purpose. And I will start with you, Dr. Siegel.

Despite advances in science and technology, the duration, cost, and failure rates of clinical trial costs have grown exponentially, leading to delayed access and higher costs for patients. How can we reverse these trends?

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RPTS BAKER

DCMN ROSEN

[10:59 a.m.]

Dr. Siegel. Well, I think there is a number of topics that have been touched on today that could help address the issues around duration and cost and failure of clinical trials. Those would include the establishment of networks that can allow one to plug in, either through trials such as Lung-MAP or through a series of trials, new therapies, and to relatively standardized approaches, with standardized startups and experienced investigators and standardized protocols. The better use of biomarkers and integrating them into trials, genomic and proteomic information to identify patient groups at risk, to identify early responders and the use of those sorts of data to adapt trials while in conduct also offer the opportunity to reach either success or failure faster with a product, and thereby to reduce the cost of product development.

Mr. Pitts. How can we improve the process by which FDA qualifies novel drug development and review tools such as biomarkers and patient-reported outcome measures, and what would this mean for modernizing clinical trial designs?

Dr. Siegel. Is that directed to me?

Mr. Pitts. Yes, Dr. Siegel.

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Dr. Siegel. It should be clear, first of all, that any sponsor or company or investigator can propose for any trial the use of a patient-reported outcome or a biomarker regardless of whether or not a patient, the FDA has qualified it. The qualification process allows a broader use and acceptability and is intended for use with -- when many groups want to come together and bring together the data that demonstrate the utility of a biomarker or a tool for a particular purpose. It does appear that that process has been relatively scantily used. I think with the creation of more consortia and networks focused on diseases, there is an opportunity to use it more. I do not have expertise in how the process might be improved.

Mr. Pitts. Okay. Mr. Murray. What part of the clinical research process consumes the most time for medical devices, and what are the major reasons device trials are moving overseas?

Mr. Murray. There is a couple reasons. As I mentioned during my testimony, early feasibility studies in getting to the point of actually having the device ready to start a pivotal study takes on average 6-1/2 years and $36 million. That is because there needs to be assessments done during the early phase. Medical devices are physical constructs and oftentimes can only be evaluated effectively in humans. So those early feasibility studies are extremely important. So streamlining that early feasibility process, IRB reviews, legal reviews for innovative new technologies can take very

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long, and having a process that is more consistent and more predictable in an environment where each site has unique and different requirements will help reduce the delays.

Additionally in today's environment we have the situation where a lot of scientifically valid data is already available outside the U.S., and the opportunity to incorporate that data and use it for informed decisions in the U.S. could radically reduce the cost.

Mr. Pitts. To pursue that a little bit, given the current reality, what can Congress do to help FDA accept the data collected outside the U.S. to ensure American patients are getting access to the American innovations sooner?

Mr. Murray. One of the opportunities is to look at rebalancing the pre- and post-market requirements. If you look at reducing slightly the confidence interval in the premarket perspective, for example, if the confidence interval in a trial were modestly reduced from 95 percent say to 90 percent in the premarket phase, that could radically reduce by as much as half the size of the clinical trials required; and as long as there is appropriate controls and mechanisms in place to continue to monitor those patients post market, that would encourage more products to be approved and could reduce the time to market.

Mr. Pitts. Ms. Stafford, how can real world data enable us to learn more about the benefits and risks of a product, both in the

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clinical trial setting and once a product goes to market, and how can electronic health records and increased data sharing play a role in this regard?

Ms. Stafford. One way that it can help in terms of using the her is actually in the feasibility of a trial and using the data that we have in the real world to help us design the best trial possible and using that data up front to even help us identify and find the right patients for the trials based on prior experience with similar drugs or like therapeutic areas. And real world is our ability to, it really goes into the master protocol or the adapted design and really bringing in data sooner and helping to make these decisions sooner based on the real-world information that we have.

Mr. Pitts. My time is expired. The chair recognizes the ranking member, Mr. Pallone, for 5 minutes of questions.

Mr. Pascrell. Thank you, Mr. Chairman. I would ask unanimous consent to enter into the record an article from the New England Journal of Medicine by Drs. Darrow, Avorn and Kesselheim, and also a statement by Ms. DeGette.

Mr. Pitts. Without objection, so ordered.

[The article follows:]

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[The prepared statement of Ms. DeGette follows:]

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Mr. Pallone. Thank you. I wanted to start with Dr. Kesselheim. Some of you have cited the need to use novel or alternative trial designs as a way to modernize the way clinical trials are conducted, and I want to learn more about one of these in particular, the use of surrogate end points. We have heard a lot about this recently, most notably with the situation surrounding two drugs, Avandia and Avastin, and these drugs were allowed on the market based on a surrogate end point through FDA's accelerated approval pathway.

So I would like to ask you, Dr. Kesselheim, to explain to us a bit more about what surrogate end points are because I am not sure I totally understand what they are and how they are used in accelerated approvals. Specifically, what are the benefits of using surrogate end points? What are the drawbacks or concerns, and how has FDA relied upon surrogate end points appropriately, or have they relied on surrogate end points appropriately in your view?

Dr. Kesselheim. Well, a surrogate end point is when we are testing a new drug or a patient wants to take a new drug or get a medical device, they are most interested in extending their lives or improving their symptoms or other kinds of real clinical end points. A surrogate end point is an end point that is not one of those end points but might predict that end point ultimately. So in the case of a diabetes drug, instead of a drug showing that it improves life span or reduces cardiovascular events, it might change the hemoglobin A1C value, which

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is a biomarker and a surrogate end point that may predict ultimately down the line what happens. The goal of using surrogate end points is to try to shorten the span of clinical trials that are necessary to test a new product.

The problem is when a surrogate end point isn't connected to the final clinical end point and then doesn't predict the final outcome of the drug, and if a drug is approved on the basis of a surrogate end point, then patients may experience bad outcomes even though their AIC is slightly improved or in the case of the tuberculosis drug, even though their sputum is slightly cleared, more cleared of tuberculosis.

So surrogate end points, in order to be used as a basis for new drug approval, need to be validated by being linked clinically, and that is a very difficult and long process and can vary depending on the particular surrogate end point. You know, just take statins, which is a cholesterol-lowering drug, and most people understand, most people agree now that lowering your LDL cholesterol is a surrogate end point towards ultimately lowering your cardiovascular risk. Unfortunately there are some cholesterol-lowering drugs like statins that do a good job of that and then are connected to with surrogate end point does predict clinical outcomes. There are other cholesterol-lowering drugs like Ezetimibe which lowers your LDL but then is not necessarily connected to improved health. And then there are other cholesterol drugs like Torcetrapib, which is a drug that raised your HDL level that

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again which was thought to act as a valid surrogate but then ultimately did not end up demonstrating actual clinical effects.

Mr. Pallone. But what about whether you think that the FDA has relied upon these appropriately?

Dr. Kesselheim. So I think that the FDA has a very difficult job and relies on surrogate end points in certain very, in certain limited circumstances where either, A, the surrogate end point has been validated or B, there is a great unmet clinical need. And that was as in the case that you mentioned, the Avastin for metastatic breast cancer case, where everybody believes we need more therapies for metastatic breast cancer, and this appeared to be a good surrogate.

Unfortunately it later turned out that it wasn't, and it increased mortality of patients with breast cancer. And the problem was at that stage it was very difficult for the FDA to then withdraw the indication and now to try to change clinical practice away from using the product because the surrogate end point had sort of caught on.

Mr. Pallone. It is difficult for the FDA to know when they are valuable or not, in other words?

Dr. Kesselheim. Right.

Mr. Pallone. Let me just ask one more. I am running out of time. Dr. Meyer, you noted that you would caution against shifting confirmatory efforts to the post-approval setting. Can you just expand upon that a little, and what is your view on how FDA has

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approached the reliance on surrogate end points.

Dr. Meyer. Okay. So as far as the proposals to shift the regulatory decision-making more towards the end of phase II relying on real world data for efficacy, I don't think we are at a point with the science where we can rely on that. The kind of evidence we want for assuring effectiveness of a drug at the present time I think can only come through well-conducted, generally randomized trials. I think the fact that half the drugs that fail from phase III to approval fail for efficacy reasons is a good example that even at the end of phase II where there is a lot of promise, that may not be confirmed by randomized control trials.

As far as the FDA's reliance on surrogates, I think on the main, they do a reasonable job on it. I agree that they are in a tough position there, but I think for the most part, they are very judicious about it, and while they may not always get it right, I think the public health balance is such that you would want them to do well most of the time, and I think they do well most of the time.

Mr. Pallone. Thank you. Thank you, Mr. Chairman.

Mr. Pitts. The chair thanks the gentleman. I now recognize the chairman emeritus of the committee, Mr. Barton, 5 minutes for questions.

Mr. Barton. Mr. Chairman, I have not been here for the -- I listened on TV, but I wasn't here in person, so I am going to pass,

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but I appreciate your courtesy. I think this is a good panel, and I think the issues they are putting before your subcommittee are excellent, but I appreciate your courtesy.

Mr. Pitts. The chair thanks the gentleman and now recognizes Dr. Burgess, vice chair of the subcommittee, for 5 minutes.

Dr. Burgess. Thank you, Mr. Chairman. And again, thanks to our witnesses for being here today.

Mr. Chairman, before I get to questions, I just want to add another unanimous consent request that yesterday's Wall Street Journal, the article by Peter Huber, they did a collection of articles about how things could change in this country to improve things. In addition to the Tax Code and two-parent families, here was an article by Peter Huber about unleashing molecular medicine dealing with the very issue that we have before the committee today. I would like to put that into the record.

Mr. Pitts. Without objection, so ordered.

[The article follows:]

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Dr. Burgess. Dr. Herbst, let me ask you a question. You touched on it, but you didn't get much chance, so perhaps you could expound on it a little bit, the use of the laboratory developed tests, I think you put it, the regulating diagnostics for clinical trials?

Dr. Herbst. Right. So this is a big challenge because right now for genetic testing there are 20,000 perhaps tests you know that look at 4,000 conditions. There are many different tests. So how are we going to regulate and develop the right tests to use? In the master protocol we have done is we are using a next generation sequencing platform which is allowing us to look at 250 different genes prior to the trial and then assort those patients to one arm of the trial. So that is an example of where we have designed the test in with a trial; hopefully the whole principle of regulation will then occur, that we will approve the drugs with the test. So that is the hope.

Dr. Burgess. Now, with the FDA reauthorization that we did 2 years ago, and thank you, Ms. Stafford, for recognizing that achievement. Nobody else paid any attention to the fact that there was a bipartisan, bicameral work done by Congress in an election year that actually worked, so I appreciate the recognition. When we did that, did that allow for the type of flexibility that you are requiring for these laboratory developed tests? Do you think as you use this next generation sequencing, that you will be able to get through the regulatory requirements that you need to?

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Dr. Herbst. I believe so. It is a challenge because this is a new paradigm to do a multiplexed series of tests and then use the data from that to put patients on trial, but the benefit we have in this large public-private partnership of the master protocol is we are working very closely with the FDA and with the branch that regulates these diagnostics and getting advice from them. We are working closely with our pharma partners, and we are working closely with the group that we have chosen to do the diagnostic tests, so hopefully we are meeting all the requirements of that should this work and should a drug actually show efficacy, we can then get these tests approved. But I think it is important to look very carefully at what test is being done, the method, the validity, the reproducibility of those tests because there are so many different ways of testing for the same thing.

Dr. Burgess. Correct. That was actually one of the unanswered questions in FDASIA, so I would appreciate your feedback to this committee. If you find it is working well or not working well, we actually need to hear from you on that, because we never actually came and closed the loop on that and came to a conclusion.

Dr. Siegel, let me ask you a question and your company, and this is a little off topic for you because you were primarily talking about drug approvals, but on the device side, Johnson & Johnson just achieved finally a FDA approval for a device called SEDASYS that assisted in the administration of analgesia and anesthesia for people who are

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undergoing minor procedures. Minor, by definition, is someone else's procedure, but undergoing procedures that are not open procedures. Can you speak a little bit to the difficulty, because that was what 17, 18, 19-year old regulatory process that this device required, and it seemed pretty simple and straightforward. Can you speak to that at all? Are we better now than we were the last 17 years?

Dr. Siegel. I think that SEDASYS is an excellent device and an important medical advance. It did raise important questions because in a sense, it is replacing the use of anesthesiologists in some cases, or at least it had the potential to replace use of anesthesiologists with a technology-guided approach to delivering anesthesia and ensuring that the patient is safely monitored. And that I think raised a lot of safety questions with the FDA. So I think the FDA had some legitimate concerns. I think it would be fair to say that there were times in the process where those could have been handled, communicated better, handled a bit more expeditiously so that the process would not have drawn out as long as it did.

Dr. Burgess. Well, the idea behind giving people a predictable pathway going through this process was largely because of the experience that your company had, and I hope FDASIA actually has dealt with that.

Time is short, but Ms. Stafford, let me ask you, you have it in your written testimony. You didn't get a chance to really get to it,

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but the sharing of precompetitive data, how is that working out? How is that approached? Can you give us some real world examples of how that works?

Ms. Stafford. Thank you. It is a very good question. In terms of the precompetitive data, it is having access to electronic health records so that we are able to take that data and de-identify it. We don't want to know who the patients are, but we want to know how to find the physicians who have those patients and enroll them. The biggest time driver in this process when we talk about these 7 to 10 years of development is actually finding the patients. And when we talk about why do we go outside the U.S., it is partly to find the patients in a time frame in order to be able to get these products to market.

And so the precompetitive, if you will, data is really having access to data to help us find the right patients for the right trials in as rapid a time as possible. Right now on average, you know, anywhere from 10 months to 4 years, and, you know, there have been trials that have been put together, and there has been some proposals put forward and the ability to use data and to recruit the patients into a trial in 14 days. And just think about the amount of time that would be cut out of the trial from 4 years to finding patients down to 14 days because we have the data that gives us access to identify the patients.

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Dr. Burgess. Mr. Chairman, I have additional questions, and I would ask unanimous consent to be able to submit those for the record. I will yield back.

Mr. Pitts. All right. The chair thanks the gentleman. I now recognize the gentlelady from California, Ms. Capps, for 5 minutes of questioning.

Mrs. Capps. Thank you, Mr. Chairman. And I thank you all for your testimony today. You know, providers and patients alike are relying on clinical trial data to ensure that we are getting the right treatment at the right doses at the right time. However, for too long these trials have not necessarily been representative of the population at large. And, Dr. Kesselheim, I have a couple questions to ask you about this, but I wanted to just highlight where I am going with my questions. Women have been excluded, assuming that women are "men with hormones." Even lab rats in the past have all been male, and recent past. And diverse ethnicities have been underrepresented. And even when these groups are included in trials, often there are too few participants in these groups to analyze the effects on them or the analysis are simply not run or reported. More and more we are hearing about how disease manifestations can diverge based on gender. Recently there was a 60 Minutes story examining how some drugs affect women and men differently.

The story highlighted an example of the drug Ambien which

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metabolizes differently in women than men. Because of this, women have been unsuspectingly receiving high doses of the drug for over 20 years. This FDA changed was followed by a report entitled Sex-Specific Medical Research, Why Women's Health Can't Wait, which provides compelling evidence for the further inclusion of sex and gender in scientific research.

And the FDA's own August 2013 report which was initiated by the inclusion of my Heart For Women Act in the FDASIA legislation show that there is still much work to be done to make sure that women are fully represented in clinical trial and that the safety and effectiveness of information is readily available.

And to you now, Dr. Kesselheim, Brigham and Women's has been a leader in research on sex differences of disease. Can you tell us more specifically about the importance of ensuring proper analysis of drugs and devices on a diverse population, and what more can NIH, FDA, and private companies do to ensure that we don't have another Ambien situation?

Dr. Kesselheim. Thank you very much for bringing that up. I think it is a really important point, and I think the essential issue that your question goes to is the generalizability of the study and for a clinical trial for a newly approved drug or device to be truly generalizable, which is to say useful in the patients in which the drug will be used after approval, it needs to have representation of both

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sexes, people of different minority groups, without relation to their financial status or their sexual orientation or any kinds of things. The problem is, is that as we move in this conversation towards talking about more efficient trial designs and other kinds of processes to try to shrink the premarket study, what that inherently does is it reduces the number of patients in which a drug or device is tested in and so makes it even harder to achieve the kinds of goals that you are talking about and that have been recognized as being a problem in medical device trials of women underrepresented in device in trials of cardiovascular devices or in trials of new drugs that will then be used in those patient populations.

It is the same for older patients, and it is the same for younger patients. I think that Congress, just as it can put, encouraged the FDA to take up, you know, innovative clinical trial designs, can also encourage the FDA to make sure that the trials that are being delivered to it are fully representative of the patient population in which the drug or device will be used.

Mrs. Capps. Great. And I want to get another topic in real quickly for you because your written testimony also touches on the sentinel system under development by the FDA to conduct post-market passive surveillance of drugs and devices to spot issues like adverse drug interactions quicker. And I believe that the sentinel program holds great promise. That is why I worked to get the Assurance For

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Defective Devices Act included in FDASIA to continue progress on the program and ensure it would be designed for drugs and devices. So can you discuss, there is only a little time left, how the sentinel program could be complement to the data derived from premarket clinical trials?

Dr. Kesselheim. Well, the sentinel initiative as you describe is a very promising pathway to try to get signals of safety issues for newly-approved drugs and soon devices as well after they are approved. The problem is that the essential work in the sentinel system of distinguishing the signal of the safety event from the noise of everything else that is going on with the drug in this post-approval observational setting is really very, very hard. So in the last 6 or 7 years, the sentinel initiative has been focused on the methods used to try to do this and has made relatively slow, steady, little progress, but steady progress, in trying to assess these kinds of methods.

There is still much, much more to be done before we can rely on the sentinel initiative for any sort of real active surveillance, and I think that that is far in the future, but unfortunately at this point my understanding is that the funding of the sentinel initiative is still up in the air, so I would encourage Congress to continue to fund it. But I would also not get people's hopes up that the sentinel system is going to provide this great white knight from a post market surveillance point of view for drugs that are approved on the basis of limited pre-market study. I think the FDA itself still refers to

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the sentinel initiative as the mini sentinel pilot program now 6 or 7 years out from its creation.

Mr. Pitts. The chair thanks the gentlelady. I now recognize Dr. Murphy from Pennsylvania for 5 minutes of questioning.

Mr. Murphy. Thank you. I want to ask particularly about a couple of the issues related to psychiatric drugs. Certainly, many medications you have brought up with regard to some recommendations for advancing the speed of these are important, but in particular, with 60 million Americans affected in some level with psychiatric illness, 10 or 11 million with severe psychiatric illness, and about 3.6 million who are not in treatment in part because of whatever the reason be with medication, et cetera. Would there be some change in the recommendations you would make to advance or speed up research with regard to psychotropic drugs, and I will open that question to anybody. Nobody has any? Go ahead.

Dr. Meyer. Yeah, I will at least try to touch on that. I agree that it is an area of great unmet medical need. I think the problem has been a couple of fundamental issues. One is how poor some of the neuroscience is in predicting targets that are amenable to becoming drugs, or targets for drugs. The second, though, is that these trials are exceedingly difficult to conduct, and, in fact, if one looks at drugs for antipsychotics and/or depression, even very well-conducted clinical trials often fail for effective drugs. So it is probably one

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of the more problematic areas to think about new paradigms of drug evaluation at the current time. I do think where the hope is for the future is really a better fundamental understanding of neurobiology to identify true opportunities for targets.

Mr. Murphy. Let me add to that. Ms. Stafford, you also mentioned I think in your written testimony about issues involving, we should be looking at some of the EU standards, and perhaps that would help expedite. I know right now part of the discussion is also in terms of TTIP in looking at this Transatlantic Trade Agreement, and those standards, I believe, should become part of that. Do you have any insights for us that you can provide with regard to some of the differences between the American FDA and the EU standards for advancing clinical research?

Ms. Stafford. Yes. I was specifically talking about the adaptive licensing pilot that was started in March, April of this year, so it is early stages in terms of Europe. And, you know, the FDA is having that discussion as well, so I don't think that they are too far behind, but I think encouragement to also pilot, there are a lot of different terms for this, progressive authorization, adaptive licensing, et cetera, and so, you know, that is the one major area that I was speaking to.

Mr. Murphy. Thank you. I also have a question with regard to the HIPAA laws and how the interpretation of those may interfere. I

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know some other members asked questions on this, but I also have some further comments of this, of how perhaps there are some barriers in what HIPAA laws are preventing us from getting information that would be extremely valuable in advancing research. I would open that up to anybody if anybody would like to comment on changes. Dr. Siegel?

Dr. Siegel. I think since the time those laws were passed, we have had a lot of experience with them, and we have new types of information that can be collected in laboratories, and I think it is time for a relook. It is important that privacy be protected. I believe it can be done in ways that also facilitate the advancing of research. And I know that HHS actually had about 3 or 4 years ago an advance notice of public rulemaking that looked at both the IRB process for patient safety protection as well as the process for privacy protection. There is a lot of opportunity, I think, both to increase patient protections, while at the same time, allowing better availability of important medical information, whether it is minimal or no risk to patients.

Mr. Murphy. Thank you. Dr. Herbst, do you have a comment on that?

Dr. Herbst. I guess one of the benefits of doing the genomics in the context of a clinical trial is then you actually have the informed consent from the patient. You are matching them to the therapy, and then you have their consent to do the discovery within the trial,

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hopefully identifying new targets for the future.

Mr. Murphy. Do you think some of this is misinterpreted now by researchers or by physicians who are just afraid to go anywhere with it because of the HIPAA laws?

Dr. Herbst. I think people are concerned, appropriately so, and they file them, and you do have to look very carefully at what consent you have whenever you are asking a question with tissue. But, no, I think people are very aggressively trying to study what they can, reconsent patients when they can also, so that we can match genomic markers to activity.

Mr. Murphy. Thank you. Dr. Khosla.

Dr. Khosla. Yeah. I just wanted to add when you talk about clinical trial networks and consortia, I think that is where the HIPAA laws may need to be modified, particularly in what Ms. Stafford was referring to in terms of kind of the pre-trial process. So before the subject has signed any consent forms, the electronic health record would need to be searched to identify participants at a given site. Currently that data can't leave that particular medical center to be merged into data from other centers.

So modifying that to allow that in a way that still protects patient privacy but allows for better ascertainment of potential participants at different sites would be very helpful.

Mr. Murphy. Thank you. So the HIPAA laws as they stand, they

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were designed to help protect patients from exposure of confidentiality? They weren't designed to hamper research in other movements. I thank you very much. I yield back.

Mr. Pitts. The chair thanks the gentleman. I now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. Green. Thank you, Mr. Chairman, and Ranking Member Pallone and for our witnesses here today.

In a time of historic opportunity offered with big data and scientific advances and technological developments it is important to examine the ecosystem of clinical trials. Before us is the prospect of transitioning from reactive systems centered on large patient populations, large clinical trials, and one-size-fits-all approach to a proactive system, they can target smaller, specific patient populations, advance personalized medicine, and revolutionize the way we prevent, treat and cure disease.

Dr. Siegel, clinical trial development in the area of antibiotics has been increasingly difficult in recent years because of the FDA trial design requirements. For instance, FDA requirements at trial study infection sites in the body versus the deadly pathogens that cause these infections that make conducting trials in the United States near impossible in large part because of the small population associated with these illnesses. How important is it to trial design successful trials, is an FDA empowered to accept alternative trial requirements

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based upon the unique nature of the disease and the patient population? By the way, I am sharing this question from Congressman Gingrey and I who have legislation working on it. So is there something that we can do that would make it easier on the smaller populations?

Dr. Siegel. Well, clearly infectious diseases are a major medical problem and threat to our country because of the rapid emergence of resistance and of new infections and because industry efforts in this area have somewhat decreased, in part because of difficulties in pathways. But I think the issue before us is the pathways that have traditionally been used and the way these drugs have been studied is, in fact, to develop them rather broadly for use, broad spectrum antibiotics for use in large populations. And as your question presumes, what is needed is a better effort to focus on specific needs to develop drugs that can be used in specifically the populations that need them so that resistance is less likely to emerge, and to have innovative pathways that will allow that to happen and allow there to be ample incentives for investment in developing those therapies. I do think that there have been both legislative and regulatory moves in recent years in that direction, and I think that that is very welcome to, in fact, ensure that there are both incentives and pathways for more targeted treatments of critical infectious diseases.

Mr. Green. Anyone else? Dr. Meyer.

Dr. Meyer. Yes, thank you. I have actually worked on this

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issue, published on this issue, and actually I would say that FDA has shown some movement. I think one of the quandaries for FDA, however, is if they accept a smaller data set on a limited population for, say, a particular infectious agent, they don't really control the practice of medicine, and the issue for them is if they are reasonably assured that it works in that population but they don't want it broadly used either because of poor antibiotic stewardship and/or uncertainties about its general efficacy and safety, they don't have a good means for doing that. So I think that is part of the consideration that might be thought through in terms of approaching antibiotic drug development especially.

Mr. Green. And I agree in the real world of practicing medicine, but the FDA can put restrictions and advisories and things like that, so physicians may not, you know, use that particular drug for things that may not be proven on the label, but I know they don't have that ability in all the doctor's offices.

So, Dr. Siegel, your testimony brings up the potential for continued recognition of surrogate end points by the FDA as having great promise for continued drug development in the United States. Over the past few hearings and roundtables, you have heard of the dire lack of new diagnostic tests for many of today's illnesses and conditions. As the adage goes, if you want to cure something, you first need to be able to identify what it is. Dr. Siegel, since such tests operate

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largely against predetermined end points, could early FDA recognition of diagnostic end points for the purpose of clinical trial design improve the efficiency and success of those clinical trials?

Dr. Siegel. First, I want to say on record that the FDA program for accelerated approval has been a tremendous success. There is a large number of drugs, especially in cancer and HIV infection, that have come to patients much sooner, a large number of effective drugs that have come to patients sooner and a large amount of increased investment in those areas. There have been cases, as has been pointed out, where subsequent studies have shown that those surrogate end points did not predict benefits.

That, in my mind, is the evidence of the success of the program, the ability to learn in the post-marking situation, and, in fact, we have found when you just look at the numbers and the implications of the drugs involved, the benefits of those programs have tremendously outweighed the risk, the downside suggesting that more use, even though it would incorporate more risk, would be appropriate.

Diagnostic tools are critical to do that, diagnostics to identify the right populations and as you indicate, to measure end points. The use of diagnostics have been limited. The technological advances in proteomics and genomics and informatics offered the powers of explosive use -- Dr. Herbst referred to some of that use in Lung-MAP -- in all aspects of clinical trial designs. And I think that investment in

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research in that area and investment in ensuring that we know how to integrate in both the research process, the product development process, and the regulatory process, we know how to integrate the development and the regulation of diagnostics with drug products is important since historically they have been done by separate organizations or companies.

Mr. Green. Mr. Chairman, I know I am over time, and I appreciate it. This is such a great panel with so much information, if you all have responses to not only my questions but other ones, please share them with us. And I thank you, Mr. Chairman.

Mr. Pitts. The chair thanks the gentleman, and I now recognize the gentleman from Illinois, Mr. Shimkus, for 5 minutes of questions.

Mr. Shimkus. Thank you, Mr. Chairman. I too appreciate you coming and have been in and out, but actually have been around in these little anterooms and stuff. But I want to start with Dr. Khosla. In your testimony you state, and I am just going to quote, that the current clinical trial for randomized double blinded clinical trial clinical trial may not be the most effective model, particularly for early phase studies. And then in the case of antibiotics, when you use -- I am really struggling with this, and I have actually been looking on my phone for the Hippocratic oath and issues. So if you are using a double-blinded placebo-controlled test, and you have someone, and I use the term "emergent condition," and they are maybe because it is

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a test you are using a placebo, doesn't that really cause ethical problems and challenges?

Dr. Khosla. Yeah. I think you raise a very important point, which is the use of placebos in trials where effective medical therapy exists, and I should clarify that there have been enormous changes over the years in what is allowable and ethical to use as a placebo. So historically, for virtually all diseases, there were randomized controlled placebo trials. More and more in my own area of expertise, for example, in osteoporosis, where we now have effective drugs to prevent or treat osteoporosis, instead of a placebo, often there is a standard of care drug that is used; and the burden of proof is to show non-inferiority or superiority to the current best treatment.

So that is a great point that you raise, and it is in the context of where there may or may not be effective alternative therapies available.

Mr. Shimkus. I am going through this because one of the statements, and this is a modernized version. I will prevent diseases whenever I can. Prevention is preferable to cure. I am to care adequately for the sick. And when we are in a system like that, obviously we are not if it is placebo.

Dr. Siegel. It is important to note that the use of placebo in a clinical trial doesn't mean that the patient is not receiving a treatment. For example, with a new cancer drug if there is already

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two drugs being given, and a new drug comes along, some patients may receive all three. The others may receive the first two, but also a placebo so that there can be blinding as to which treatment, but they are still getting fully standard treatment. Placebos can be very important in research but should not be equated with lack of treatment.

Mr. Shimkus. Seems like this started some comments, and so, Mr. Murray, please.

Mr. Murray. Yeah. So medical devices, it is a very important moral and ethical question. And there are instances for breakthrough medical devices where there is not an existing therapy, and you do a surgical procedure, especially with an active device that is not turned on, so the person is not receiving therapy. That, I think, adds to the conundrum, if you will, and I think it becomes a major challenge that is unique for medical devices especially in those breakthrough areas where there is a treatment-resistant diseases with no other options.

Mr. Shimkus. So let me go back to Dr. Khosla real quick. As far as in this process that we just discussed, any other FDA reviews or reforms that you would suggest that would be helpful in this process?

Dr. Khosla. Well, I think it really comes on a case-by-case basis depending on the particular disease being studied because for certain diseases there are effective cures, and you are really looking for a drug that might be better or have fewer side effects, and in that case,

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clearly the use of a placebo isn't warranted. In other instances, there really isn't a good alternative and the standard of care may involve, you know, for example, just giving nutritional supplements like vitamin D or calcium. And in those instances using an active drug against that standard of care is appropriate. So it is a major ethical issue. It is something, though, that is very specific to each disease entity and the alternates that are available.

Mr. Shimkus. Great. Thanks. And for my final minute, let me go to Dr. Siegel, and you talked about proteomics, if I pronounced that right, and molecular diagnostics and genomic sequencing. So what do you believe Congress needs to do to address and ensure that the potential for, I guess the terminology is precision medicine can be realized by both developers and clinicians?

Dr. Siegel. I think the potential to utilize those technologies in the development of precision medication is critical. I don't know that there is a specific legislative need to change the rules or the way drugs are developed. I think that we have what we need in that regard. I do know, however, as we have seen with breakthrough therapies, that congressional attention to an issue, highlighting an issue, congressional exhortations, congressional direction of how Federal agencies invest and spend their money can have a big impact, and I think in those areas certainly enabling FDA and NIH to help enable those technologies and those developments could be very important.

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Mr. Shimkus. Thank you. And I know, Chairman, you probably have asked and will mentioned that there will be opening record for questions. There may be follow-up questions based upon your response. We would solicit and then we would forward to you. If you would do that, Mr. Chairman, I would appreciate it.

Mr. Pitts. Yes, we will have follow-up questions. The chair thanks the gentleman. Now I will recognize the gentlelady from Florida, Ms. Castor, for 5 minutes of questioning.

Ms. Castor. Thanks to the panel for sharing your insights today. Dr. Meyer, I know you were formerly at the FDA and you have worked in industry, so I would like to get your insights based on that experience on a couple of questions. We have heard a lot today about various ways that clinical trials can be modernized, everything from increased use of technologies like electronic health records to increased use of alternative trial designs like surrogate end points and adaptive trial designs. A lot of what has been mentioned I would assume is outside the purview of FDA. I imagine a lot goes on in the development of drugs and devices that doesn't and shouldn't involve FDA at all. I would like to hear your view on that. Do we have the right balance for the modern era?

Dr. Meyer. So I think some of what we have been hearing is outside the purview of FDA. For instance, the use of electronic health records for precompetitive screening of patients and understanding who the

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patient populations might be. That really is preregulatory as well. I think the expansion of the use of surrogates is clearly within the FDA's purview. I think the difficulty there, though, is not with the FDA. It is really identifying biomarkers or other assays that will be validated to predict outcomes. That is no easy task, and it sometimes takes a very, very long time. If you take for instance, Alzheimer's disease, everybody would like to be able to do much smaller, much more focused trials, but to date, the biomarkers we have have not predicted benefit. So there is no choice but to do large, long trials.

I think the other thing that I would say is that the FDA does, I think at times, have some reluctance to accept things like a patient-based electronic assessments. And I think that is something that they could be encouraged to do. I am not sure it needs legislation, but for instance, if you are a pulmonary patient and you are able to have a very reliable home spirometer and measure your air flow every single day, that is a very rich data source. But if FDA insists that those patients go into the clinic and be assessed in the clinic, that is actually inhibitory to patient enrollment to some degree, but also I think it produces a more expensive and complex trial.

Ms. Castor. Mr. Murray, do you think that the current regulatory scheme is meeting the entrepreneurial spirit that is out there? And I will give you a great example. In my home town of Tampa, we have a fantastic new center called the Center For Advanced Medical Learning

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and Simulation by the University of South Florida. I was so proud of it, I took Mr. Pallone to visit, and I know Mr. Bilirakis has been there where we are bringing together the medical engineers, the academics, the folks that can work through the business cycle, have the 3D printers right there so they take the device right to the 3D printer right into a computer analysis of whether it works or not. Does this regulatory scheme currently, is that going to be acceptable for the advances in technology and devices?

Mr. Murray. Excellent question. The genesis of MBIC was the recognition primarily from Dr. Jeff Shuren at CDRH and the commissioner that medical device technology is advancing at a rate that we have never seen before. You see it in the consumer and the mobile and the social media side, but you are seeing that translate over to health care as well. So there was a recognition that tools methods and approaches used needed to evolve, and to do that we are working collaboratively in the precompetitive space. And you mentioned 3D printing. That is an example where you are going to see the realization of personalized medicine where using computational modeling and simulation, people will be able to have tailored custom devices that fit them and meet their needs specifically.

Where we are going right now, and I think the opportunity and the need, and we talked about this in terms of HIPAA and data, but there is a tremendous amount of data that is available out there in terms

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of patients' post approval of devices, and if you will, if you had the opportunity for, we have right now donor selections, if we had people that would be data donors instead of organ donors, and they would allow their data to be used, I think we could improve by orders of magnitude the quality and richness of those models and simulations to even improve more on the technology that is going to realize personalized medicine advancements.

Ms. Castor. Thank you very much.

Mr. Pitts. The chair thanks the gentlelady. I now recognize the gentleman from New Jersey, Mr. Lance, for 5 minutes of questioning.

Mr. Lance. Thank you very much, Chairman Pitts. In the various testimony of members of the panel, you have discussed the challenges in attempting to coordinate the work of multiple institutions before and during clinical trials. Varying regulations and protocols make it difficult, I think, for institutions to communicate one with another. If institutions that are attempting to coordinate have difficulty doing so, what about those that are not working together, and what methods are currently in place, if any, to reduce redundancies in clinical trials, and what steps would the panel recommend to ensure we are not doubling up on research or making the same mistakes over and over again. Dr. Siegel, yes.

Dr. Siegel. Well, there has been a lot of advances recently in terms of transparency of research results and rapid publication, and

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there has been a lot of growth of consortia, TranCelerate Pharma as an industry consortia, various other broader groups to enable better communication and cooperation. I think that you have heard from several members of the panel. One area, though, of better shared learning and cooperation that we see already but could see more of are disease-specific clinical trial networks and trials, such as Lung-MAP or organizations which bring together broad expertise. And one of the nice things about some of the newer approaches to that is that there are organizations that are not just, say, academic centers coming together with perhaps government support, but are also incorporating patient and industry expertise and input to enable better addressing of some of the operational problems as well as the scientific problems that they need to face.

Mr. Lance. Thank you. Dr. Herbst.

Dr. Herbst. Yeah. I would agree with that. And just sharing our experience for the lung-MAP trial, we are looking to accrue a thousand patients a year, and this is throughout the United States, really focused at the community, places that normally don't have access to these types of trials. So it really requires using the National Clinical Trials network, and that network uses a central IRB. We heard about that from the panel, so that this trial doesn't have to go through a different IRB at each site, which can takes weeks in some cases. So that is very helpful. I agree with Dr. Siegel, the commitment and

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working with all the partners, the Pharma partners especially, you know, the National Clinical Trials Network is being supplemented by the public-private partnership that we are working with. We need to all work together with the FDA as well because this would all be a failed effort if at the end of the day, these drugs and marketers couldn't go for approval of the drug. I think one thing we all have to also consider we heard a little bit about surrogate end points is quality of life and patient-reported outcomes and how we are going to build those into the trials and work with patient advocates and with those groups early on.

Mr. Lance. Thank you. Yes, Doctor.

Dr. Khosla. I just wanted to reemphasize what I had mentioned in my testimony, which is that NIH is investing in these clinical translational science awards across the nation, and so this is a preexisting network where there are going to be best practices incorporated over time. There is hopefully going to be increasing IRB reciprocity, so many of the obstacles that we have heard about hopefully will be reduced or eliminated. And it isn't disease specific, so it would be open to any disease for which there is a trial ongoing.

Mr. Lance. Thank you. To the panel, is there something more we should be doing here on this committee and at the Federal level to make sure that this occurs in the greatest way possible for the benefit of the better health of the American people? Yes, Dr. Herbst.

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Dr. Herbst. Getting back to the whole idea of the public-private partnership, I think it is essential. In my, opinion that is one of the reasons the Lung-MAP is working well. Any way the committee could work to incentivize that to move forward the precompetitive measure. The fact that we have five different companies deciding to put their hat into our trial versus doing a trial themselves. I would hope that at the end of the day, they will see this is the only way to find these small populations of patients. But they are taking a risk, and ways to sort of incentivize, to promote, to give them credit for that, I think would be important.

Mr. Lance. Thank you. Yes, sir?

Mr. Murray. And again, on public-private partnerships, but in particular with our partnership which includes NIH, CMS, FDA, the ability to have a flexible collaborative environment in that precompetitive space, it is oftentimes very structured -- I think its FACA, if you will, that becomes an important consideration. So we have to be able to foster and encourage these kinds of partnerships in that precompetitive arena.

Mr. Lance. Thank you. Yes, sir?

Dr. Kesselheim. Another thing that I would add is that I guess I am a little bit less optimistic than Dr. Siegel is about where things stand right now in terms of data transparency and the ability to share clinical trial data, and I think that this committee and Congress can

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do a lot to try to encourage and put in place systems and structures to allow sharing of clinical trial data to try to prevent redundancy in testing of new drugs and to try to allow different groups to learn from data that is currently right now held as a trade secret by many companies.

Mr. Lance. Thank you. My time has expired, and it is been a very interesting and informative hearing. Thank you, Mr. Chairman.

Mr. Pitts. The chair thanks the gentleman. I now recognize the gentleman from Louisiana, Dr. Cassidy, for 5 minutes of questioning.

Dr. Cassidy. Dr. Siegel, the sharing of the data, it is proprietary data, so is the obstacle to the sharing the company releasing it? I am just asking.

Dr. Siegel. Obviously you need to have some protection of proprietary information in order for innovation to occur, in order to have incentives for innovation. However, when clinical trial data get to the point where what is learned about that data could be used to protect the safety of patients if it is a drug that is already approved or there --

Dr. Cassidy. I accept that, but just in terms of expediting other research. I am just intrigued. Sounds like a great idea but will the companies agree to it? Do you follow what I am saying? I am not arguing either point. I am just asking.

Dr. Siegel. We have put in place through an agreement with Yale

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a third-party review that will enable much greater access to our clinical trial data where needed for important medical research in patient safety, and we believe that that is not incompatible at all with protecting innovation and allowing --

Dr. Cassidy. I think it was the Michael J. Fox Foundation that in order to receive their grant, you had to collaborate prior to peer review publication. Maybe I have that wrong, but nonetheless it seems like a nice concept. I don't know the practicality of NIH. Does NIH require that? I don't believe they do, do they? Anybody.

Dr. Kesselheim. I am not 100 percent sure. I would also support what Dr. Siegel has said about his company and its innovative relationship with Yale is actually quite a good model for other companies, but it is relatively rare at this point. I think that the NIH when it funds research, you know, should be held to the same standard as when companies fund research as well. But when research on products that are available in the market is done on patients, there is really no reason why that research shouldn't be available for further study and for greater learning by everybody.

Dr. Cassidy. Dr. Herbst.

Dr. Herbst. I will just add that Yale and NCI Comprehensive Cancer Center, and I do know that the new regulations for recompeting those grants do require even more collaboration between centers, so hopefully through that we will bring the Pharma partners, too.

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Dr. Cassidy. Dr. Khosla, you and others mentioned having a centralized IRB, but that is already allowed. The Western IRB is the central IRB for many others. Now, would Mayo cede their, knowing how prestigious Mayo is, would they cede their IRB approval to a centralized western IRB, for example.

Dr. Khosla. I think the answer to that is that is a culture change that is occurring at many academic medical schools.

Dr. Cassidy. So let me ask, that is merely a culture change. There is nothing regarding statute or regulation. I am asking because it seems like there is a certain institutional pride that some institutions do not wish to cede. That truly seems more a culture issue than statute or regulation. Is that correct?

Dr. Herbst. Correct.

Dr. Cassidy. Believe me, I am from that culture. I understand the hideboundness of it. Now, you also said something which I found intriguing. Dr. Herbst shook his head yes, that if you are doing the screening with genetic markers, that material, that information has to remain domiciled with the institution, and yet Southwest Oncology Group, I am just asking, you have multiple institutions. If one of them has certain biomarkers, they cannot share that with the centralized, whoever is overseeing the entire study framework. Whatever you learn cannot be shared with that centralized authority.

Dr. Herbst. Actually yes and no. First of all, the patient gets

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their data, so that is very important. So we are making this screening available to patients where they might not have had it or afforded it. And then, of course, the excess tissue does get banked through the cooperative group structure. That is not part of the national system.

Dr. Cassidy. Now is that statute or legislation? Does that require an act of Congress? Oh, my gosh.

Dr. Herbst. No, no. The groups have tissue banks and the tissue goes in the tissue banks, and with petition anyone, it is a public bank, can petition the swag at some point if they have a study and they want to use this tissue.

Dr. Cassidy. Dr. Khosla, I think what you said is that if you do biomarkers, those results remain at the institution and cannot be shared with others. Did I hear that correctly.

Dr. Herbst. No. Maybe you misheard me. This all goes centrally. In fact, the whole beauty of this is we are profiling at 500 different places with the same technique where it all goes through a central database. And that is the beauty of it. The point I was trying to make is we have very broad consent on these patients all very carefully through the IRB so that we are both putting patients on the drugs that we know now may or may not work. We are also able to discover new targets so the next four or five drugs that will come into the Lung-MAP we will be able to be more informed in what we choose.

Dr. Khosla. So just to clarify, what I was referring to was the

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preparatory to research phase so before the patient's actually been enrolled in the study to search the electronic health record, identify patients at a site, that information, before that patient has signed a consent form, can't leave that site.

Dr. Cassidy. That is okay. I used to do clinical research, and I had 10 patients who I knew were interested in a trial. We knew from looking at their study. It is just that they had not had the formal testing. I don't see that as a impediment so much, and I forget if we did this. If it is illegal, I didn't do. But nonetheless, I would say listen, I have 10 patients whom I think we can enroll as soon as we start. There would be some sort of signal, knowing that it didn't guarantee, but it suggested it might happen. Is that an impediment?

Dr. Khosla. It is an impediment to the extent what when you have these national clinical trials networks, it is sort of an ongoing process to recruit both a site investigator and the study participants. And so if you know up front where the patients are, then you can seek out individual investigators at those sites. So in that sense, it is an impediment.

Dr. Cassidy. I yield back. Thank you for your generosity.

Mr. Pitts. Chair thanks the gentleman. I now recognize the gentleman from Virginia, Mr. Griffith, for 5 minutes for questioning.

Mr. Griffith. Thank you, Mr. Chairman. I appreciate that. I am going to pick up on that real quick. There is a company out of

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Richmond that I have been real excited about. It is not in my district, but it is close enough. It is the The Health Diagnostic Laboratories, and what they do is do all the stuff on your blood looking mainly at heart disease and diabetes. I am sure they can add to their form a consent in advance, because what they are doing is tracking biomarkers and giving counseling to the people they have done the blood work on, obviously with the oversight of the physician. But they are giving counseling and trying to help folks avoid heart disease and diabetes, and a lot of times those biomarkers are overlapping.

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[12:00 p.m.]

Mr. Griffith. And just seems to me that that might be a good place. Because they have got folks all over the country that they Fed Ex in their blood samples to and they -- I call it the Henry Forded blood lab work. And it is really exciting stuff. And it just seems to me that might be something you all can look at and find a way, particularly if they get consent from their patients in advance, you might be able to track some of the biomarkers that you are looking for or some of the other things that you all are looking for that you then can get rid of that impediment that you were talking about by having a whole slew of folks automatically identified who may have already given advance consent at least to be contacted.

Ms. Stafford. I was going to say, I think the operative word is "consent." And as several of us have discussed, it is a matter of designing your consent up front that allows you that capability. And, you know, for instance, we have a tool, a technology, MediGuard.org where we have about almost 3 million patients that we have data, we have a relationship with. But we consent them, with them to participate in real world research with us, et cetera.

So I think it is about the consenting and what you put in that

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up front.

Mr. Griffith. Absolutely. I would never want anybody's information being shared without their consent.

What do you find in your getting the consent up front? What do you find? It was about 5 or 10 percent that say they don't want their data being passed along?

Ms. Stafford. I don't have the metric. But it is interesting how many people want to be in the conversation. How many people are members of different, you know, groups like the ADA, American Diabetes Association or multiple sclerosis, and where they find their communities and how interested they are in research opportunities.

And so our database is really, you know, do you want us to communicate with you? Because they are all very interested in being part of research.

Mr. Griffith. And you all mentioned it earlier in your testimony today that, you know, the technology and things are moving so much faster than it used to move, and it is exciting and really has great opportunities.

I want to switch gears a little bit, although it does connect. You know, I think about these issues of developing new treatments. And I have to tell you, I align with the mindset of those who support right to trial laws that are being passed in the States. And I have introduced similar bills, two such similar bills here for patients

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whose doctors have exhausted current medical options, have been told that the end of life is nearing. My feeling is, why should the Federal Government interfere if the patient wishes to spend their own money on experimental treatment plans? I have this saying, if I'm dying anyway, why do I need to be protected by the FDA? Because death is near. And all treatment options have been tried.

That being said, I think the issue of benefit/risk framework should be brought forward in the earlier stages of a study of a new treatment by allowing an informed and responsible access to medications after the establishment of safety could allow for a faster translation of the science and technology from lab to clinic while insuring safety benefiting patients, and at the same time, leveraging our nation's leadership and investment to advance science and technology.

One of the bills I have introduced, the Patient Choice Act, does this by creating a provisional approval process after drug safety has been established to allow patients to have access to new treatment while the efficacy is still being tested. This is similar to how things are moving in Europe.

I think this makes sense. I think it makes sense to empower a patient, as we have been talking about today, particularly faced with the dilemma of a terminal disease, to help move the ball down the field in the area of medical science and medical knowledge about fighting to save their own life with experimental drugs if they choose to do

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so. And even if they fail, the satisfaction of knowing that they may have helped save someone else's life.

So then the question comes, because I know that a number of you, particularly Dr. Meyer, are generally opposed to this kind of a concept. But when you are faced with the subset of that terminal patient, and their doctors have indicated that the current medical options have been exhausted, how do you tell that person that they can't spend their own money to try something that may not work but that might hold some promise? Dr. Meyer.

Dr. Meyer. So I would actually like to address that very point. Because actually from my experience at the FDA, it is usually not the regulators who are standing in the way of that. It is actually more often the companies. And there are a couple of considerations around that. Often they cannot charge, and going through the mechanisms to charge are very arduous. And they have to prove what their investments have been.

The other thing is that it ends up dirtying their data, if you will. So you mentioned the patient maybe having an altruistic view of even if I don't benefit, maybe others will. But unless they are in a trial of some sort and their data collected in a rigorous fashion, they may not, in fact, contribute meaningful data to the evaluation.

So I very much am sympathetic to that view that those patients who have no other options, and there is a promising drug out there,

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should get access to it. But I think it really requires a thoughtful look at the ecosystem around that, if you will. And, you know, what is the problem, what is the fix.

Mr. Griffith. Mr. Chairman, I know my time is up. I know Mr. Murray wants to respond as well. But I have to yield back at this point.

Mr. Pitts. Go ahead, Mr. Murray.

Mr. Murray. Thank you. I just would say patient choice we believe is an important aspect, and also the consideration for devices in that discussion. And to the extent that there are methods and methodologies to streamline how a patient may pay for a procedure, because that is a difficult aspect in this, especially if it is in a clinical trial, and how adverse data might be considered if it is not in a controlled environment.

Mr. Pitts. Chair thanks the gentleman.

Now recognizes the gentlelady, Mrs. Ellmers, from North Carolina, 5 minutes for questioning.

Mrs. Ellmers. Thank you, Mr. Chairman. And thank you to our panel.

Ms. Stafford, I have the great honor and opportunity to be representing North Carolina. And certainly, your operation and organization there, the world headquarters right there in Durham. And I just have a couple questions for you. Again, obviously, our goal

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is to try to make the system work more efficiently so that we can get these very important drugs to market in a much quicker, efficient manner that is safe and, you know, for all of our constituents.

And my understanding, as we have learned about the clinical trial path that the sponsors who are collecting the data, they have to collect so many end points, I mean, dozens of end points. And, you know, to demonstrate that the drug is safe and that it works. My question to you, in your opinion, I mean, how much -- how much data do we need and are we collecting too much data? Is the data we are collecting truly efficient or are we collecting so much data that it is just over in abundance? And can we find a process to narrow that down if that is the case?

Ms. Stafford. Thank you for your question. And of course, I am wearing my North Carolina blue, just to say.

Mrs. Ellmers. Yes.

Ms. Stafford. Anyway, it is a very good question. And I actually, I am a statistician by training. And I have seen in my 30 -- almost 30 years in this industry now, we collect too much data. There is too much collected. And a lot of that comes from the multiple voices at the table.

And I do think that having the conversation up front, and I think the FDA wants to work with us on this with the industry. But there are a lot of key opinion leaders in the design of the trials, which

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includes many academic centers and scientists who have different opinions. And they want to prove that the drug is efficacious and safe, but they also want to explore what don't we know about the drug, what extra information can we get that is beyond really the investigation of that product.

Mrs. Ellmers. Again, what I think you are saying here is what we need to do is narrow the scope so that we can come up with the information. And certainly more information is great, and that can be used in many ways after the fact. But I agree. I think -- so would you say that up front, straightforward, more transparency and focus on the actual goals that are trying not to be put forward initially?

Ms. Stafford. Most panel members here talked about the trial design. And I think it all comes into the design and trying to focus the design. And, as you say, the scope and focus that scope and not enter into too much interesting extraneous data which end up taking time to collect the data. Once you have that data, what do you do with it?

Mrs. Ellmers. Then you have to do something with it.

Ms. Stafford. It is just very costly, so trying to focus the scope of the trial design is my recommendation.

Mrs. Ellmers. Very good. You know, there again, what we are faced with, or, you know, we are seeing more the trend towards global clinical trials. And, you know, here for our committee, we are looking

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at ways that, you know, we want to show incentives so that some of those clinical trials can be here and kept in the United States.

Can you pick one or two suggestions on how we can achieve that goal so that we are doing more of those clinical trials or we are kind of returning back to a process where we are doing them here in the United States?

Ms. Stafford. I think we are having that discussion today in terms of ensuring that the U.S. is at the forefront of innovation around clinical trials. And that as long as we are the leader today in clinical research, we need to maintain that by being innovative and by modernizing the clinical trial and by being in a position to stay that leader. You know, drug development is no longer a one country, one continent, or one region. But we can certainly ensure that we keep our heritage as the clinical research leader by continuing this innovation discussion.

Mrs. Ellmers. Thank you. And I saw some other nodding heads. Dr. Herbst, would you like to comment?

Dr. Herbst. Yeah, I would agree. You know, I am a medical oncologist. Many of us who work in cancer have very busy clinics. There is limited infrastructure. You know, flat or declining public money. We are bringing some of the private money in. But really anything we can do to streamline the process, you know, the burden on the staff. You ask a few more questions, that means a coordinator or

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a nurse has to spend some time. You know, fewer, you know, rooms available. We want to put more patients on trial. Putting 5 percent of patients in this country on clinical trial is way too low. We have to do 20, 30, actually everyone should go on a trial in these incurable diseases, and to do that we really need as efficient as possible.

Mrs. Ellmers. And, Dr. Khosla, do you agree with that?

Dr. Khosla. Yes.

Mrs. Ellmers. Thank you.

Thank you, Mr. Chairman.

Mr. Pitts. Mr. Murray, you wanted to add something?

Ms. Murray. I would just state briefly for medical devices, the just-in-case perspective of what is going to be required at panel for breakthrough devices and not knowing up front what a panel might ask. So bringing that part of the process forward would be very helpful. And also allowing for more flexibility in the early discovery. So when a new device comes out, you learn something in allowing for adaptive trial designs that incorporate and don't necessarily poison the data for the overall trial.

Mrs. Ellmers. Thank you very much, Mr. Chairman, for extending my time a little bit there.

Mr. Pitts. Chair thanks the gentlelady.

Now recognize the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

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Mr. Bilirakis. Thank you, Mr. Chairman. I appreciate it.

Dr. Herbst -- again, I want to thank the panel for their testimony today as well. And I appreciate you holding the hearing, Mr. Chairman. So very important.

Dr. Herbst, I am impressed with your multi-stakeholder partnership that resulted in the Lung-MAP program. Lung cancer has a 5-year survival rate of less than 20 percent. The work that NCI-designated cancer centers do is tremendous, as far as I am concerned. In the Tampa area, we have the Moffitt Cancer Center, as you know, which is the only NCI-designated cancer center in Florida. They have a partnership which has resulted in the Oncology Research Information Exchange Network, ORIEN. This is the world's largest -- in my understanding, it is the world's largest clinically annotated cancer tissue repositories and data for more than 100,000 patients who have consented to the donation for research.

In your testimony -- this is my question -- in your testimony, you mention the importance of partnerships to accelerate clinical trials as well as the need to examine the incentives structure and process to facilitate data generation sharing and collaboration. Could you briefly elaborate on this and how this should be done, please. Can you elaborate?

Dr. Herbst. Right. And I do compliment Tampa on their work. They were one of the leaders initially in doing this personalized

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medicine network and bringing it together. And we are basically doing the same thing. The Lung-MAP is really, it is a truly national effort. And, as I mentioned, it came from an NCI panel and from work at the Friends-Brookings meeting.

And the thing that is very nice about it is, we want to -- we are working closely with the FDA, with the foundation for the NIH, and others. We really want to really bring these drugs and this testing throughout the Nation to the community. So the idea basically is to pick and do profiling in one specific way at all the different centers. Within 10 days. You know, because patients can't wait, they have advanced disease. You are right. This is not -- this is even worse than what you mentioned because this is squamous cell lung cancer, mostly a smoker's lung cancer, where there really are no other therapies to offer these patients. The most advanced, widespread disease.

And then we are randomizing patients to either the standard of care or to one of these new drugs based on the molecular profile. And we have five different drugs. So the way this has worked has really been a good concept, something that the academic community, the clinician community around the country, and the drug companies and the private payers see as a very important way to move forward. And we have all worked together. And it has taken a large amount of collaboration, meetings. It really is a partnership. And I sit here now, but there are hundreds of people who have been involved in this

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process. And I am very proud of how we have all worked together. And we are doing it for the patients.

And the other thing that is very important is advocacy community has been involved with us from the very beginning. And they have advised us on some of the issues regarding disclosure and forms and consent forms. And we have really worked -- this is really focused on the patient and bringing more drugs to patients quicker.

And I just want to add, the FDA has been so supportive of this process. Of course, these trials all have to go through the standard phase II, phase III criteria. In fact, they are very strict criteria. But we have had advice as we move along: How do you integrate the markets into the trial? So I would say this is something that has to be emulated. And other diseases are already working on this. There is a trial in colon cancer that is moving forward, breast cancer, and others as well.

Mr. Bilirakis. Terrific. Very encouraging. Thank you, Doctor.

Dr. Siegel, you raised the issue of providing greater voice for patients in clinical trials. You mentioned that the investigators only objective outcome measures. The investigators. But not information from patients like how did they feel. How are they progressing. How could investigators and regulators use qualitative data when making decisions?

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Dr. Siegel. Well, thank you for that question. I think it is an important one. It is easier, I think, and that is probably why there is a history of using things that can objectively be measured in the lab or life or death. But beyond what the exception of life or death, usually what is most important is how a patient feels.

The science -- there is a science behind how to do that. If you are not careful about how you do that, you can introduce a lot of bias, you can use tools that mis-weigh and that don't really represent patient outcomes.

So that has been part of the reluctance to -- or maybe the slowness in incorporating patient-reported outcomes. With that said, I think we are at a place where they can and should be incorporated much more broadly in almost all areas of clinical research.

Mr. Bilirakis. Thank you very much. Another question for you, Dr. Siegel. Can you explain in laymen's terms what adaptive clinical trials are, how they are different from traditional clinical trials, how has FDA viewed adaptive trials? I believe they have released guidance just a few years ago. And have adaptive trials been used in Europe? And what lessons can be learned from Europe?

I am not sure if that has been covered, because I had to step out. But if you could elaborate, I appreciate it.

Dr. Siegel. Not in any depth.

So more traditional trials, you design the trial and how you are

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going to conduct it and how you are going to analyze it up front. And then at the end, you unblind the data and you do your analyses.

That offers the advantage of avoiding a lot of biases that can lead to inaccurate assessments of treatment effects.

In adaptive trial designs, you learn as you move on. You use biomarkers or actual outcomes in patients, if they are available fast enough, to understand what are the more promising therapies, perhaps, maybe putting more patients onto those therapies, changing randomization, substituting changing or selecting among doses. Or even select changing entry criteria. You could change almost any part of a trial.

A lot of scientific work has gone into how to utilize adaptive trials, because if done wrong, there are opportunities to introduce bias. But they allow real-time learning from what is happening within a trial. Therefore, they can be extremely powerful tools in drug development.

The FDA has been out in a leadership position in terms of providing guidance as to how they could be used in the regulatory setting. There is, of course, some conservatism because of the scientific challenge.

But it is an opportunity to accelerate our ability as you have heard about from Dr. Herbst, to accelerate our ability to learn within clinical trials. And I think it is one that is very much underutilized.

Mr. Bilirakis. Very good. Thank you.

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I yield back, Mr. Chairman.

Mr. Pitts. Chair thanks the gentleman.

That concludes the first round of questioning.

This has been another exciting, informative, important hearing. A lot of members have follow-up questions. So we will send those to you within 10 business days.

I remind members they have 10 business days to submit questions for the record. I ask the witnesses to please respond to questions promptly. Members should submit their questions by the close of business on Wednesday, July 23rd.

Without objection, subcommittee is adjourned.

[Whereupon, at 12:19 p.m., the subcommittee was adjourned.]