COVID-19 Evidence Accelerator: What We've Learned, Where We're Headed

October 20, 2022 | 1-4 PM eastern

Meeting Transcript

Welcome & Introduction

Susan Winckler, RPh, Esq., *CEO, Reagan-Udall Foundation for the FDA*

Susan C. Winckler (00:06:00):

Hello and welcome to our virtual public meeting to review the progress and report on all that we've learned from the COVID-19 Evidence Accelerator, and we're so glad that you could join us today. I am Susan Winckler, and I have the honor of serving as the Chief Executive Officer for the Reagan-Udall Foundation for the FDA, and we're pleased to be working with Friends of Cancer Research to be hosting this virtual event.

(00:06:49):

Before we begin, I have just a few housekeeping-ish items to review. We have a fantastic lineup of speakers today, and it is so packed that we don't have the opportunity to take questions from the audience, but we do encourage you to use the chat function to add comments or ask your fellow participants questions. Because of our meeting size, attending cameras and microphones will remain off throughout the meeting, and the meeting is being recorded and the recording, along with the slide deck and transcript, will be available on the Evidence Accelerator website next week.

(00:07:23):

To orient you to our time together, here's our plan. In just a moment, I'll turn the podium over to Dr. Namandjé Bumpus, FDA's chief scientist, who will be followed by FDA Commissioner Dr. Robert Califf, and finally, a keynote address from Dr. Amy Abernethy, the President of Clinical Studies Platforms for Verily. After that, we have three panel discussions that will collectively look at where we've been, what we've learned, and where we're headed as it pertains to gathering, analyzing and using real-world evidence. And finally, we'll close out with a chance to hear from one of the champions of the COVID- 19 Evidence Accelerator, Dr. Ellen Sigal, the chairperson and founder of Friends of Cancer Research and Chair of the FDA Foundation's Board of Directors. So that is what we are going to do as we aspire to reflect on two years of meetings and discussions in our immersion in real-world data within the pandemic and the COVID-19 Evidence Accelerator.

(00:08:28):

I'm about to step away and move to the first of our speakers. So I want to introduce Dr. Namandjé Bumpus, who is Chief Scientist for the FDA. Dr. Bumpus, I should first say welcome to the agency, although you've been there for a bit now, but we're so pleased that you could join us today. I also have to say congratulations on your election to the National Academy of Medicine. Such a well-deserved honor. Now, you are new enough to the agency that you've had the opportunity to join just one or two of the Evidence Accelerator gatherings, but we're so glad you could join us today for the public meeting, and I'm going to step out of the way and let you make a few opening remarks.

Opening Remarks

Namandjé Bumpus, PhD, *Chief Scientist, Food and Drug Administration*

Namandjé Bumpus (00:09:11):

Thank you very much, Susan, and thank you to all of you. Really good to be here with you. So as Susan mentioned, I am the Chief Scientist at the FDA. The FDA office of the Chief Scientist works to advance scientific excellence, innovation, integrity and collaborations through providing strategic and cross-cutting FDA-wide leadership, coordination, planning and scientific training that's needed to catalyze a translation of regulatory science. So through that lens and really through that scope, I'm particularly pleased to have the opportunity to engage with the COVID-19 Evidence Accelerator and to be part of this discussion today about what has been learned and what lies ahead.

(00:09:52):

From the outset, the COVID-19 Evidence Accelerator was designed as a means of helping to propose, evaluate, and problem- solve some of the potential applications of real-world data and real-world evidence to the pandemic. We intended the Evidence Accelerator to be a forum, where experts from a variety of organizations, whether academic, industry or government, could come together and share ideas and experiences.

(00:10:20):

The Accelerator then evolved into another avenue to help the agency keep pace with what was happening in the pandemic, to hear about how FDA-authorized products were being used, to gather insight into data dilemmas, and to see the real-world data community put their heads together and propose solutions. Furthermore, we benefited from hearing how groups working within this space tackled problems and concerns, whether it be issues of data, interoperability, understanding, medication use data, or coding the severity of COVID-19 in hospitalized patients.

(00:10:58):

A significant focus of the Evidence Accelerator has been using real-world data to help illustrate the performance and use of FDA-regulated products, whether diagnostic and screening tests, vaccines or therapeutics. We have learned a tremendous amount through the course of the pandemic, and anticipate the continuation of that learning, particularly through the capture analysis of real-world data. So with that, thank you very much, everyone, for attending, and I'm really looking forward to this discussion.

Susan C. Winckler (00:11:30):

Great. Thanks so much, Dr. Bumpus, and we appreciate you joining us to open the meeting today. We now want to turn over to hear from FDA Commissioner Califf, who, as many of you know, has remained committed to the role and importance of real-world evidence throughout his career. He served as a speaker during some of our early meetings of the COVID-19 Evidence Accelerator when he was in the private sector, and of course, has remained engaged in real- world evidence in all that is happening as he returned to his seat as Commissioner. So let's turn to hear from him now.

Remarks

Robert Califf, MD, MACC, *Commissioner of Food and Drugs*

Robert Califf (00:12:09):

I'm pleased to join you for today's close-out meeting of the COVID-19 Evidence Accelerator. This project is one I'm pleased to say I've been associated with since its beginnings. I've had the opportunity to both watch and participate in its development and it's very meaningful to me. I want to thank FDA's Chief Scientist, Dr. Namandjé Bumpus, who has been involved with this project since she joined FDA several months ago. Additionally, I especially want to recognize Dr. Amy Abernethy, who you'll be hearing from later, for her extraordinary contributions and leadership on this project throughout its duration.

(00:12:46):

Many of you know that if there's one guiding principle of my career, it's been my focus on the importance of acquiring and using good data. In each area of healthcare I've had the good fortune to work in, clinical practice, academic health system administration, research and public health, I've worked to strengthen the ability to generate the best available evidence and to embrace the sophisticated tools and technology needed to do so.

(00:13:13):

I firmly believe in the importance of the continuum, from data to information, to knowledge, to wisdom, but also know that while data are necessary, they're not sufficient. Data must be curated and analyzed properly, and we must continually work to increase the understanding of the value and interpretation of data at all levels of society, from the layperson to the expert data scientist.

(00:13:39):

The FDA, with its focus on science and public health, is especially reliant on having the most reliable evidence based on the highest-quality data to fulfill our mission, and of course, the challenge of doing this is that evidence is a constantly moving target, because it must always be considered in the context of an ever-changing environment. In the past decade, there's been an explosion of data related to our work. Today, data comes from many varied sources: electronic health record and claims data, direct-from-the-public data, supply-chain data, as well as the data traditionally submitted as part of medical product applications or prospective registries and epidemiologic studies.

(00:14:25):

Adding to this, the questions we are tasked with answering are more complex, but the promises are extraordinary. The application of these data to the intersection of biomedical science, technology and communication offers a potential to usher in a new era of better health for the US and the world. That's

why initiatives like the COVID-19 Evidence Accelerator, developed by the Reagan-Udall Foundation for the FDA in collaboration with Friends of Cancer Research, are important. They help us discover and manage answers to the most challenging and contemporary healthcare questions.

(00:15:03):

By bringing together experts in health data aggregation and analytics and by providing a collaborative space for different organizations and stakeholders from across the health data ecosystem, the COVID Accelerator has supported our ability to use real-world data to create real-world evidence, even as that knowledge base has continued to evolve. You'll hear many additional details about this important project during the meeting, but I'd like to briefly mention one other aspect, and that's the potential it offers as a model for enabling evidence generation throughout the product cycle.

(00:15:39):

As we know all too well, the need for evidence generation continues throughout the life-cycle of medical products, particularly as larger and more diverse populations may be considered for a medical product or have not been as well studied in initial clinical trials. Medical products also usually gain a toehold in clinical use based upon specific indications and limited, well-defined populations and traditional clinical trials.

(00:16:08):

Additionally, uses are identified in clinical practice, and in the setting of an unprecedented pandemic, word spreads rapidly. Too often today, a high percentage of clinical decisions are not supported by evidence, and the system for gathering evidence can be slow, expensive, and too focused on certain types of questions. We saw that with a proliferation of useless or dangerous treatments in the pandemic. The use of both real-world evidence and structured prospective trials eventually caught up, and brought rational care into focus.

(00:16:42):

By integrating these vast data sources to provide a more complete picture of health linked to high-quality study designs and methods, we can produce a more continuous evidence-generation system from pre- to post-market that will help develop and support a true national learning healthcare system. I want to thank Reagan-Udall and the Friends of Cancer Research for bringing us to this point, and I look forward to working with all of you as we build on this foundation.

Susan C. Winckler (00:17:14):

We so appreciate the Commissioner providing that message and for his commitment to advance the use of real-world evidence, which brings us to our keynote address. I'm not sure that any of us at the foundation or at Friends can think of the Evidence Accelerator without simultaneously thinking of Dr. Amy Abernethy. While juggling countless issues and priorities as FDA's Principal Deputy Commissioner, she found time to open nearly every diagnostics and therapeutics lab meeting and personally contribute to our parallel analysis discussions. She joined meetings from her home, her office, her car, an airport, her porch and an Uber, and probably some other locations, but always bringing her engagement, energy and focus, which helped to shape and drive the project. And she continues her work in real-world evidence. I'll hand the microphone over to Dr. Amy Abernethy, the President of Clinical Studies Platforms for Verily. Amy?

Keynote Speech

Amy Abernethy, MD, PhD, *President of Clinical Studies Platform, Verily*

Amy Abernethy (00:18:15):

Hi, Susan, and hello to all of my amazing friends here in the Evidence Accelerator. I am just so incredibly honored to be here with you today and to celebrate where we have come through this period of time. My colleague Julia Wu is going to be sharing my slides. For those of you who have been through many Evidence Accelerators meetings with me, we're always doing something new and bold right at the last moment. In this particular time, Julia is going to join us in sharing the slides.

(00:18:46):

And I really just want to say how much I appreciate Friends of Cancer Research; how much I appreciate Reagan-Udall Foundation; how much I appreciate you and all of this community who worked so hard together to figure out how to address critical questions in the pandemic through the Evidence Accelerator and the work that we did together. As soon as the slides come up, what you're going to see is my first slide.

(00:19:16):

In my first slide, what there is what we used to call the GPS. Just a little bit of background on the GPS. So what happened is as we were getting going and the Evidence Accelerator... And in case you're wondering what's going on in the background, by the way, right now, we're just trying to figure out why the slides aren't showing. So that's just trying to move along there. One more try. And while we're doing that, I'll just tell you a little story.

(00:19:49):

So the Evidence Accelerator started at the very beginning of the pandemic. Oh, there we go. One more forward, Julia. It started at the beginning of the pandemic, where what we were trying to do is think about how do we bring data, the data that exists of many different landscapes across healthcare in the US and worldwide, to start solving and addressing the critical questions in the pandemic?

(00:20:12):

And we realized that the questions were so diverse and there were so many different issues, we needed to figure out: how do we organize ourselves working together? We developed lab meetings and work streams. And in doing so, it got a little confusing. And so one day, somebody said, "We need a GPS." And so we started every meeting from that point forward with the You Are Here slide to remind ourselves, in any Evidence Accelerator meeting, why we were together and how this was coordinated into the overall book of work. And today you are here: Evidence Accelerator, October 20th 2022, where we're looking at what we've learned and where we're headed. Next slide.

(00:20:50):

And the conversation started in really March of 2020 around this critical issue that we needed data to help figure out how to solve critical questions, how to address evidence needs in the context of the pandemic. Data, data everywhere, and me without a drop to drink how do we make this work for us? Next slide.

(00:21:13):

And we really, as an Evidence Accelerator community, said, "We actually have to make sure we also create mechanisms to bring all of the sides and capabilities together." So we learned how to work together quickly, learn from each other and constantly move the ball forward without sacrificing quality, without lowering our evidentiary standards, and demanding rigor of each other.

(00:21:40):

We wanted to bring the best of what was available in the private sector, whether that was health tech, data companies or companies that were making solutions to understand and generate evidence, what was best available in the healthcare delivery and research ecosystem, whether that was academia or healthcare delivery systems or payers, and also government to make sure that we could do this in quick ways. And that was really the purpose behind the Evidence Accelerator community and it really gave us the chance to say, "Here's what I trust and here's what I don't trust. Here are the new capabilities we're going to need for the future, and here's how we built and developed those together." Next slide.

(00:22:20):

We had our first meeting in April of 2020, and as I mentioned, it got pretty confusing very quickly, but in order to do this, we leveraged elements that had been built before by Friends of Cancer Research and now took those and modified them to put them to use within the context of the pandemic. Those elements included developing an initial set of research questions: research questions really motivated by FDA, of what FDA needed in April of 2020 to move things forward, but also critical elements like: what were the data elements that were going to be needed to answer those questions and where do we need to do work to get this better? Whether that was analytic work, or for example, better definitions. I think many of them in the audience will remember all of the meetings around better defining oxygen requiring in the context of the early parts of the pandemic. Next slide.

(00:23:11):

And we also realized we had a set of responsibilities as a real-world data community. Many of you will remember what I used to call the [inaudible 00:23:20] debacle, and what that reminded us is that we really needed to develop a set of capabilities that we all understood to inform data selection and protocol design, to make sure we had transparent analysis and could cross-check each other's work, that we had the ability to audit as necessary and have informed peer review and also publications. And as a real-world data community, we saw that as our set of responsibilities and priorities.

(00:23:47):

And those responsibilities and priorities then led to, next slide, what we all developed together, which was our set of principles of how we work together. And I think these principles still stand today, and I really hope that they will continue in the evidence-generation world of the future. A few of them I wanted to highlight here: the importance of transparency. The importance of building trust, both within our real-world data community and also for others outside of the real-world data space to trust the work that we were doing. The idea that we were going to embrace and explore convergence of findings as well as discordance of findings and understand what that teaches us. Be patient and work together. Next slide.

(00:24:34):

And through this work we've been able to answer, as a community, critical research questions. I really sincerely believe not only have we asked and answered critical questions, but we've learned how to do this and it's informed critical work, such as regulatory guidance, how to, and also pharmaco-epidemiology work for the future. Next slide.

(00:24:57):

What we've seen now is for example, the real-world evidence primer that's come out of this work that's helped us understand the benefit of real-world data to compliment clinical trials, to stop talking about real-world data or real-world evidence, but real-world data add real-world evidence to solve for clinical evidence generation, and also to complement what's happening in the clinical trials space. Next slide.

(00:25:23):

It's also informed a number of cross-industry publications and learnings. So we've seen work from the Evidence Accelerator now show up, for example, in publications from the National Academy of Medicine. This critical piece from NAM looking at what we learned from digital health in the pandemic, really it was a key way of distributing our findings of the importance of bringing data to the problem and answering questions together as a community. Next slide.

(00:25:54):

And a couple of lessons learned from the front lines. These are things I wrote down as I was leaving FDA and thinking about, what did I learn from the Evidence Accelerator? One of them was the many roles for real-world data and real-world evidence. Using real-world data to help us, for example, to describe the contours of the pandemic; think about and understand supply chains; understand for example, diagnostics in the context of the pandemic. There was great interest, and continues to be interest, in real-world data to create comparator data, arms and study controls, and I think we have a lot of important work to continue to do in this space.

(00:26:33):

We also saw the importance of figuring out how to submit data sets that were not captured in a formal electronic data-capture system, and how do we appropriately have a [inaudible 00:26:43] and audit trails. We learned, in the context of the Evidence Accelerator, the importance of regulators coming to the table early and saying, "This is what I trust and this is what I don't trust," something that I called regulatory familiarity and also regulatory thinking within the context of our space. Certainly, the prospective space became progressively more important, and great enthusiasm for novel real-world evidence prospective study designs showed up in many different ways. And as we saw, there's many reasons for skepticism, whether that's a methods development or the data that are needed, but we can start to resolve those areas as we start to think about how to do this together. Next slide.

(00:27:27):

There's been continued momentum, and I look towards the many important guidances that came out from FDA, as well as regulatory guidance from around the world, much of which actually took some of the inspiration and lesson lessons learned from this Evidence Accelerator community. I feel so proud for how this community showed up and how we keep showing up, and now codified in draft guidance going forward. Next slide.

(00:27:54):

And I think really what we learned in context of the pandemic, and what I think we're going to keep seeing show up, is that there is a shift in evidence generation going on, and that story is a story that was unfolding in front of our eyes in COVID. We've moved from the landscape of formulaic Phase I through IV clinical trials to something that looks more like continuous evidence generation across the life-cycle of a medical product.

(00:28:22):

The COVID-19 mRNA vaccines really became the poster children for this story: vaccines that were authorized and approved on perhaps a smaller corpus of information with shorter clinical trials with fewer number of people, but where we understood our responsibility to be reflective of all people, representative of our population, and then use information that continued to evolve in real-world settings to understand critical questions like duration of effectiveness. Can you mix and match vaccines? When do you need a booster? What about our children? And those kind of questions really played out in the post-authorization, post-approval setting, and really have become the best exemplar of what it looks like in the new evidence-generation landscape of our future, the figure on the right.

(00:29:15):

So with that, I want to close and again say thank you. A huge and a hearty thank-you for this community. Hard things are hard but worth doing. Over to you, Susan.

Susan C. Winckler (00:29:27):

Amy, thank you so much. You've reminded me how great it is to be in a session with you and to just hear the way you can package information and remind us of all that has happened here in COVID-19 and within COVID-19 Evidence Accelerator and that applicability in real-world data and real-world evidence.

(00:29:49):

So now we'll move to our first panel, and I'll say, as we announced at the top of every COVID-19 Evidence Accelerator meeting, the Foundation and Friends convene the community at the request of FDA. So it's important to hear the agency perspective, and to guide that discussion, I'm going to turn it over to our constant collaborator and partner for the Evidence Accelerator, Jeff Allen, who serves as President and CEO of Friends of Cancer Research. Jeff, would you pick it up?

Session One: FDA Perspectives on the COVID-19 Evidence Accelerator

Moderated by Jeff Allen, PhD, President and CEO, Friends of Cancer Research

Sara Brenner, MD, MPH, Center for Devices and Radiological Health, FDA

Jacqueline Corrigan-Curay, JD, MD, Center for Drug Evaluation and Research, FDA

Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA

Jeff Allen (00:30:20):

Absolutely. Thank you, Susan. It's great to see everyone. Good afternoon. As Susan said, my name's Jeff Allen. I'm the President and CEO of Friends of Cancer Research, and on behalf of our organization, I certainly want to thank Susan and the team at the Reagan-Udall Foundation for the opportunity to collaborate with all of you during this evolving effort, as Amy so well described that in her remarks, and

certainly thank FDA for their partnership in this endeavor as well, and the many, many different partners that have participated in this initiative over the last couple of years.

(00:30:54):

I think, as Amy mentioned in her remarks, this has been an evolution, really demonstrative of many different sectors being willing to come together and share information. And I think the strength of this collaboration was really that it was done in partnership with various different sectors, a great deal of expertise, a great deal of openness and collaboration, and willing to share data at all different points on a variety of different topics.

(00:31:25):

So I'm thrilled today to have the opportunity to expand our discussion with several leaders from the FDA. So joining us, as you can see on the screen here, is Dr. Sara Brenner, the Chief Medical Officer for In Vitro Diagnostics, and the Associate Director for Medical Affairs at the Center for Devices of Radiological Health, or CDRH, at FDA; Dr. Jacqueline Corrigan-Curay, the Principal Deputy Center Director at the Center for Drug Evaluation and Research at FDA, or CDER; and Dr. Peter Marks, the Director of the Center for Biologics Evaluation and Researcher, or CBER, at FDA. Thank you all for joining us.

Jeff Allen (00:32:03):

CBER at FDA. Thank you all for joining us today for this discussion and to share your perspectives on ways that you and your colleagues within each of your different centers were able to interact with the community through some of the initiatives in the evidence accelerator. As Amy mentioned at the outset of her remarks, this was an activity that really started with an attempt to bring together various different disparate sources of information. And I hope that was successful in an informal manner. We really thought about some of these weekly meetings as lab meetings for those of us who grew up in the laboratory sciences, the idea of being able to pack up your lunch and come and informally share data and ask questions and respond to those questions, receive those criticisms, and improve hopefully the work at the outset was really the thought that we could be able to do this.

(00:32:53):

And I think it exposed us to a great deal of different community members that were able to come share their experiences at a really uncertain time. So maybe to kick off our discussion today, I'll start with a question to all three of you. Really thinking back as we kind of track our experience with this evolution, thinking back to those early days of the pandemic where decisions were having to be made on a relatively limited information base, given the novelty of the situation that we all found ourselves in. So if you think back to that, what were some of those missing pieces of information that were particularly challenging in those early first few months, and how do you think the external research community was able to help fill any of these gaps, including how FDA was able to engage? Maybe Dr. Marks, I'll start with you if you don't mind, and then we'll move to Jacqueline and Sara.

Peter Marks (00:33:50):

Yeah. No, thanks very much, and thanks so much for hosting this. And I think Amy did a really great job of introducing this topic, so thank you. Early on there was so much uncertainty over so many different things related to the epidemiology of what we were seeing in front of us and related even to the natural

history of disease, how long it lasted, what kinds of people were going to be most susceptible to it. And some of that got clarified reasonably quickly, but then came very quickly with the initial attempts at therapeutics, we really had very crude methods to try to figure out what was going on. There were some IND studies that were started up with various things including convalescent plasma, and I think it was lucky to have some of the academic collaborators who were at least collecting data on what was going on in individual hospitals at the time, to be able to understand, at least in case series of what was going on in individual hospitals or in individual care systems with COVID-19.

(00:35:24):

But there were real gaps there of not being able to understand a lot of fundamental things, and at least having initial evidence was helpful. But as we speak about it, there were things that probably could have been done better in a collaborative manner back then, but at least having those data helped us somewhat. I'll stop there because others may have other perspectives on that.

Jeff Allen (00:35:56):

Jacqueline, maybe I'll turn to you to see if you have additional thoughts on how this type of activity was able to fill any specific gaps early on in the pandemic.

Jacqueline Corrigan-Curay (00:36:09):

Sure. Well, again, thank you for hosting this. And I just want to applaud Amy and RUS and Friends of Cancer for really having the vision to bring this. This was really unique. It was brought together quite quickly at a time when we really did need and we continued to need to always be leveraging all the data that we can and to have just very smart people in the room and taking a very sort of deliberate and thinking about the quality of the data, thinking about the quality of evidence, questioning I think was really important. So as Peter said, we really didn't know a lot about risks, clinical manifestations, what the burden of the disease was going to be. So having a forum for information sharing and expert discussions certainly at the beginning was so important and to have that conversions. I know that Amy talked about these case definitions and fundamental principles, which are so important if we're going to use these kind of data to really think about how are we doing it and how are we doing it right so we get some useful information.

(00:37:17):

We learned about new data sources, technical developments. There was I think some more partnerships that were able to get us rapid analysis of data that we might not have had through our own systems when we went into the pandemic. Even as Amy talked about supply chain, it was through the accelerator, we started to get some data as Peter was saying about the medications that were being used for these critically ill patients and what was being used and how much was being used in what order. And for us, that was very important to have that insight because not only are you thinking about therapeutics which had to be developed, but you're thinking about let's make sure we have the supply of the drugs that are needed right now and what do we do, what is going to be needed and how do we take that information and start taking actions to make sure the supply chain remains robust.

(00:38:13):

And then I think the other thing is really to continue that effort, we started to see different things in the pandemic and how it evolved and our early understanding then new things that we understood. I mean, I think very early in July, I was looking back on my notes, the accelerator was already talking about persistent symptoms and long COVID. So I think you were really always raising these issues very proactively. And I think for a regulator that's really important to be able to try and see things earlier and then try and plan what to do. So I'll stop there.

Jeff Allen (00:38:50):

Thank you. Sara, the addition of diagnostic testing was a quick add on to the accelerator's activity and certainly an area of complexity that I would gather, it's still one being worked on. Any thoughts from you about some of the early challenges that these types of collaborative experts and data sharing exercises were able to help inform?

Sara Brenner (00:39:15):

Yeah, you bet. Thanks so much Jeff, and it's a pleasure to be here representing CDRH. I've been at the front lines in the Office of In Vitro Diagnostics since the beginning. So taking us back to the January, February 2022 timeline is when diagnostics was called on to go out of the gates immediately, of course, because IBDs being distributed were our eyes on the virus. And so I think it was a great addition to add in vitro diagnostics to the evidence accelerators because it started early. It started first out of the gates, and then it's still going on today with a rapid evolution of emerging technology in a highly distributed diagnostic testing landscape that will service tip of the sphere for a variety of other conditions. But if I were to take it back then, some of the challenges that we anticipated early on were things like how are we going to scale testing, at what volume of testing is going to be up with the pace of spread and will Central Labs have the infrastructure that's needed to do that type of testing for the whole of the country?

(00:40:17):

So these were challenges that we were aware we were going to need to deal with from the very beginning with the test work. What were the EUA authorization processes going to look like? How would we work across the inner agency? And then thinking ahead on data, since Annie brought that up, and we've enjoyed working with her in the past and the evidence accelerator team from then on. One of the things about diagnostics, and we'll talk about this more as the panel goes on, is that we had the knowledge that if we're going to try to use diagnostic data to keep track of what's happening with viral spread throughout the pandemic, we're going to need methods for capturing high quality, consistent regulatory grade of possible data from highly distributed diagnostic testing networks. And that infrastructure, quite frankly, we knew did not exist at the outset. And so we were going to have to not only look at UA applications in our office, but things like supply chain, things like new types of IT and technologies that could capture and transmit data at scale.

(00:41:22):

So to do that, working with states has been critical and working with a variety of different stakeholders, including public health labs and clinical testing locations, et cetera, was going to have to happen. So having an evidence accelerator approach was really helping us to fit those needs because through the course of sort of the bread and butter of regulating medical products, we don't always have

opportunities like this to engage with a broad array of stakeholders who we need to work with, and we need to hear with in terms of what their challenges are, what they're seeing across the country, coast to coast with regards to testing needs, testing challenges. When we started to scope out diagnostic data testing elements, there was a balance of how much data is too much and becomes too burdensome versus what's the minimum set of data that is extremely high utility for clinical decision making, for regulatory decision making, and for public health policy making. So all of those things were things that we talked about on a very frequent basis through the evidence accelerator program. And for diagnostics that was critical, and it's been ongoing and spun off many projects that we'll talk about later on. But for now, I'll turn it back over, Jeff.

Jeff Allen (00:42:35):

Great, thank you. Maybe a follow up question, I'll sort of go in the reverse order in case anyone wants to jump in here, but I think you've touched on this a little bit in terms of some of the, you've obviously mentioned some of the specific areas that were dealt with. And in the early days of assembling these groups of experts and different data sources and research communities, I think there was a joint desire to try and sift through a lot of information of varying different quality that was of constantly churning and at a time when everyone was disrupted to some extent and more than anyone could have anticipated, but really wanting to, as Amy said, kind of crowdsource and try and help. So in that type of general approach, how unique was this? Was this filling a unique niche for FDA and with FDA that perhaps, or is this type of engagement something that's typical?

Sara Brenner (00:43:41):

You want to go backwards this time?

Jeff Allen (00:43:42):

I'll go backwards. We'll start with you.

Sara Brenner (00:43:44):

Even though I just went on for a while, so I'll be brief on this, and turn it over to colleagues. But yeah, I would say that this is unique in the sense that it's orchestrated and supported by staff who we have a regular cadence of engagement. There are presentations, there's structure around information sharing. We have other ways to do that in the center and I'm sure in other centers, but sometimes, and especially under pandemic conditions, public health emergency conditions, we, our staff lack the bandwidth to orchestrate these types of things and to really follow through on them. And that's a high maintenance activity because when you bring together these really high powered intellectual private sector and public sector players, there's rich dialogue and a lot of information that can be shared. So it takes the type of effort and the type of really, I'll call it an aggressive approach because the timelines were aggressive and the engagement cadence was very fast. And that helps our center staff tremendously. I would say otherwise we wouldn't have the bandwidth to engage in these types of activities to the extent we did.

Jeff Allen (00:44:51):

Jacqueline, anything to add from your perspective?

Jacqueline Corrigan-Curay (00:44:54):

Yeah, I think I could just echo that. I mean when you think about where we were at the beginning or just even the first year now sometimes, we were so focused on working with sponsors, getting all the working on supply chain, working on all the questions, the clinical trial conduct, that we would not have been able to have the bandwidth to organize something like this. And we certainly weren't going to stop and host a meeting on RWE and COVID. We wouldn't be able to reach out to this many people. So having this forum that you did such great quality work in thinking about what were the important issues to bring to us and to have us to be able to just, it's on our calendar, someone can go, and I think we made it a priority. We would talk, if you can't go, I got to go. We've got to listen to what's going on and really understand because we knew we could learn from this.

(00:45:56):

And it really did help prioritize some of our thinking about real world evidence. I mean that we got very involved in the natural history coagulopathy study. I mean that was a real priority for us. And so seeing these, being able to just come to this meeting, have you organized, bring these experts together, show us who's working on what, what's the data, where are we finding the challenges, where is it working? Was just incredibly invaluable.

Jeff Allen (00:46:27):

Peter, anything to add?

Peter Marks (00:46:28):

Yeah, I'm going to just end up echoing this. I mean, I just want to just, not to put too fine a point on it, but we were just trying to stay afloat for the several months of the first months of the pandemic where the regulatory work that was coming through in terms, some of this was just pure paperwork for expanded access programs was crushing. And yet it was so important to have substantive interactions around really important medical topics. And I think without this opportunity, this venue to have rich dialogue, we wouldn't have been able to support it. So I think this really filled that niche really in a way that we had no way to at the time.

Jeff Allen (00:47:14):

It was a very interesting, it continues to be a very interesting ecosystem to imagine having real world discussions with some regular groups of experts that I think interact with FDA and the community on a regular basis, such as various hospital systems and research communities. But I can remember sessions with school systems and professional sporting associations to understand what they were seeing through some of their various efforts, and hopefully that could be informative as well. Jacqueline, maybe I'll move to you and thinking about how these types of data sharing and regularly being able to have different sectors kind of share their experience on COVID-19, how did that help inform the utilization of real world data into regulatory decision making?

Jacqueline Corrigan-Curay (00:48:11):

So as you're aware, we've been using real world data a lot for many years for our safety assessment, but then along comes the new disease that you don't even have an ICD-10 or nine code for. And we, having this dialogue very early with experts in defining how best to really get at the data that we need to monitor was quite informative, and it certainly spurred some collaborations. And we also needed real world data to accelerate our understanding of the disease. And sometimes that might guide the design of clinical trials. If you really don't know what's going on in event rates, it's very hard to design a good clinical trial. We have been focused on trying to find that, as Amy said, this complimenting where is real world data best to compliment other evidence that we're taking in for effectiveness? So those kind of dialogues were happening before COVID.

(00:49:10):

And I think having these conversations really informed as we went back, I mean we published several RWE guidances during the COVID pandemic. So really being involved exploring the challenges has involved, informed our thinking. And I think as we go on, we begin to think about how real world evidence once you have something. So once you have something on the market, then you've lost equipoise you're not going to do a clinical trial. You know you need real world data to sort of inform what's... Because the virus unfortunately doesn't seem to stop mutating so we have to figure out are we still seeing benefit? And I think understanding and thinking about what does high quality data look like in that setting, especially because we know that once you're on the market, those who get a product and those who don't get a product can differ.

(00:50:05):

But I think we saw some really nice inspiring, and I think it was at one of the groups, I think for Mayo that showed their system that not only was looking at how do you get access for patients from monoclonals, but setting up an infrastructure that was also capturing the kind of data.

(00:50:22):

So you were constantly informing your understanding. So I think there was a lot of dialogue that this is the way you move towards what we hope to get to, which is the learning healthcare system. You're getting the access, but you're collecting the data. And so I think we're going to continue to need real full data throughout this pandemic as we continually reassess the benefits of what we're doing.

Jeff Allen (00:50:48):

Thank you. Sara, any thoughts From the device and diagnostic experience?

Sara Brenner (00:50:55):

There are many directions that we've expanded into, we'll say, with regards to exploring how to leverage real world data and evidence for diagnostics and for other medical devices as well. So one of the challenges we had at walkthrough with different stakeholders as part of the evidence accelerator was how to converge data streams to understand things like real world IVD performance and capturing core diagnostic data sets, which is what we call the standardized set of SARS-CoV-2 IVD data that we were able to standardize during the pandemic before pre-market and post market throughout what we call total product cycle of the IVD is phenomenal. It's a phenomenal opportunity to evaluate the

performance of the device over time. But if we can combine it with other data, other medical countermeasures data, other device and medical product data and importantly clinical data, then we have a much more rich context to understand a variety of different ways that the use of these devices, SARS-CoV-2 IBDs are actually impacting patients and clinical outcomes.

(00:52:07):

It also gives us better insights in terms of population health. When we're talking about testing, of course, there's a benefit for the individual patient and potentially a benefit for the public in a population health sort of way. We're able to use diagnostics to monitor the spread of disease, for example. So through the evidence accelerator, there were many partners who came in from the clinical world, and we talked to them about the challenges and opportunities of looking at different types of data sets and how to align those and integrate them, or at least look at them side by side and say, how can we as an agency, as part of our mission space be more informed about how these products are being used and how they're performing under real world conditions for real people and what impact do those things have on real patient outcomes?

(00:52:55):

So those are bridges that are difficult to cross traditionally for FDA, I think, and especially challenging under emergency conditions. So in any event, I guess that's just a lot of agreement with what Jacqueline said. And I'll turn it over.

Jeff Allen (00:53:10):

Thank you. Peter, I guess particularly on the vaccine side of things, certainly also not an area that has not previously leveraged real world data. Obviously for safety, it has been something for many years. Has the pandemic experience with real world data provided any additional experience on monitoring other aspects of the vaccine performance?

Peter Marks (00:53:38):

Yeah. So it's a great question. And actually it's really interesting because our folks actually had been working using real world evidence for vaccines before pandemic with influenza. And it's actually some people from our biostatistics folks and Epi folks who did work with high dose influenza vaccine showing that real world evidence could reproduce a randomized clinical trial because when you're dealing with randomized clinical trials that have tens of thousands of people and databases that have millions of lives and outcomes that are hard like hospitalization, you actually can do real world studies with vaccines. And actually, it's impressive that the reduction between conventional dose, influenza vaccine and high dose influenza vaccine found between the real world evidence study and the randomized clinical trial were very similar about 20, 22%. And the real world evidence actually gave firmer endpoints. So we knew that this could be done.

(00:54:53):

And I think during the pandemic, we've seen time and time again, real world evidence coming to the rescue, whether it was real world evidence gained here in the United States or in Israel or in Scotland or other locations on vaccine effectiveness. And that has been really important in real time or near real time as we are dealing with this constant succession of variants because it's giving us some idea of what

we might expect from the vaccines that are being deployed and the boosters, et cetera, in this setting. So I think we've come to realize how important real world evidence is here. And in fact, the importance is highlighted to us by the limitations we have because of some issues with immunization information systems that limit us. We realize how much more we could do if we could overcome those limitations. So we really appreciate the ability to use real world evidence in this setting. And I think even since COVID, we're using it now for Monkeypox, so it's becoming something that's kind of a standard tool of the trade.

Jeff Allen (00:56:21):

So those are really helpful examples. Thank you. Sara, maybe I could come back to you for just a minute. You mentioned in some of your earlier comments about an evolving infrastructure in terms of coding and having access to information around specific diagnostic testing. As different tests and technologies have been deployed over the last couple of years and continue to evolve, could you expand a little bit more on some of the opportunities that you see sort of this enhanced infrastructure that's underway as an initiative of CDRH and others, ways that real world data could sort of help inform the sort of long-term understanding of performance?

Sara Brenner (00:57:08):

Yeah, you bet. So it's been quite an odyssey in the diagnostic data space, but to try to summarize, I'd mentioned before early out, before we even knew or didn't want to think that SARS CoV-2 would become pandemic, we had the sense that if it did, we would need to have a core or a standardized harmonized diagnostic data set so that the data flowing from all tests would be harmonized, interoperable and get somewhere that someone could do something with it. So we were able to establish that under HHS authorities. And then we sort of understood that the volume of testing that would be conducted initially in central labs would eclipse what states were typically used to handling for public health testing. And the states would be the first portal that would receive COVID test results, and then they would flow up to the federal government.

(00:58:06):

So as folks are probably aware who are dialing into this call, one decision was made early on to stand up a diagnostic data or a COVID data, I should say, infrastructure HHS Protect. And so we wanted to ensure that diagnostic data that was harmonized, we would be able to flow through states up into, in a de-identified way, HHS Protect. So agencies like FDA, CDC, NIH, Asper or others would have access to that data in as real time as possible. So that was a heroic effort that many colleagues of mine worked on. And I was fortunate enough to be simultaneously detailed up to HHS for two years to stand up the diagnostics piece. But it was massive, and it required states, it required private labs, it required public health labs. And then the next turn that we anticipated on the horizon was the need to move testing out of centralized traditional brick and mortar laboratories to keep up.

(00:59:07):

And so by that time we were already behind, the virus, but in any event, we were working as quickly as we could to authorize point of care tests and then soon after, over the counter tests. And so the point of care and over the counter testing space, removed the physical in vitro diagnostic device from the lymph system or the data capture and transmission systems of brick and mortar labs. Seeing that that was

likely where this would go if we needed wide scale, highly distributed testing, we immediately began working with developers and other innovators in the community through innovation sprints and through individual reviews and through messaging communication and also through the evidence accelerator to figure out how can technologies, digital health tools, apps, websites, be launched with over the counter and point of care diagnostic tests so that there is a way for data to be entered by the patient or the user or the person administering the test and have that wirelessly packaged and transmitted into a state health department or HHS protect.

(01:00:09):

So we were simultaneously working on the point of capture, which is the IBD hardware software, digital health tool integration and the receiving portal. Because if you're going to pitch, you need to have a catcher. And so that data was going to have to flow in real time, wirelessly from anywhere. That's never happened. And so we worked really hard with folks across the inner agency to create interfaces and portals that could receive harmonized data, and let that data flow into Protect such that it could be analyzed and interpreted alongside the lab-based data. So that's still very much a work in progress. And I think, just to be fair, we didn't keep up. Okay. We tried and we built things that hadn't ever been built before, but there's an enormous amount of testing that happens over the counter now, and that data's not captured. So the testing eclipsed our ability to capture that data, but the opportunity is there and we are capturing a percentage of it. And so we are learning a lot about what the benefits and the opportunities are versus the limitations of self collected testing data and how to interpret and analyze that alongside clinical laboratory data. There's tremendous opportunities that we can see, from our office anyways and in working with stakeholders, private sector who are developing tests for all types of things beyond SARS-CoV-2 to really improve patient access to testing and the utility of diagnostic data. But of course the quality of those tests matters a lot. It is critical. So a test is only as good as the result that it gives you. If it's the right result, fantastic. If it's not the right result, this is a problem.

(01:01:55):

And so it's this balance of quality and understanding performance along with speed and access and all of these things. And then folding in the additional data capture element. Outside of the pandemic and outside of reportable diagnostic conditions, diagnostic tests conditions like infectious diseases, the data from a test performed for another condition, including things like chronic disease monitoring would still need to get somewhere. We'd still need to get to a clinician or a healthcare provider to make a decision on. So in any event, these are enabling technologies that we hope will be lifting all those moving forward. Turn it over.

Jeff Allen (01:02:32):

That's incredibly helpful, thank you. I'll pause and just see if Jacqueline or Peter have any thoughts on that information flow, challenges from the therapeutic or biologic side of things. And it's a little different.

Jacqueline Corrigan-Curay (01:02:46):

Yeah, it's a little different. Well, EUA medications, we're able to track them, we're able to track how they're being used. I think there's probably not the same. These are not over the counter, so we don't have that issue with it. I would say that. But what we really see that's important is having real time data

as much as possible so we can really understand are they being used, who are they being used for? Where should we be targeting education? If we're seeing of adverse reactions and drug reactions, what education do we need to get out? And then of course, as I said, once these drugs are on the market, we increasingly will have to, as things evolve, try and measure the best that we can, that the benefit continues. I think that's a priority, a continued priority.

Jeff Allen (01:03:47):

Great. Thank you. I'm sort of thinking a little bit into the future here. Maybe Peter, I'll start with you on this one since you mentioned earlier on in your comments that particularly those early several months were...

Jeff Allen (01:04:02):

Those early several months were very heavy in terms of the workload in different processes and things like that. Now that we realize that the pandemic is a part of everyday life and a continuing part of healthcare, how is it a continuing part of FDA's workload and has there been the ability to get back to a regular cadence with all of the other things that you all are overseeing?

Peter Marks (01:04:34):

Yeah, great question. So certain areas have gotten back towards normal. I'd say essentially, our areas where we're dealing with blood products, cellular therapies, gene therapies are starting to get back to more normal situations as development get...

Jeff Allen (01:04:59):

I think you hit mute [inaudible 01:05:01]

Peter Marks (01:05:01):

Oh, sorry, you weren't able to hear me before. Oh my goodness, my finger wandered. So certain thing, our cell gene therapies, blood products have been able to get back on target and things are moving. On the area of vaccines, we are still very much under a very large load of work. That's because we're dealing actually with the after effect now of having... In the therapeutics end, even in ours, many of the things that were under EUA ultimately went away because they didn't work or because no one wanted to take them further. For us now, we have a cohort of products that seem to work, vaccines, and we know work actually that we have to bring forward to licensing. And so we have the wave of licensing actions that have to happen, plus we have new vaccines coming along in the COVID-19 space and potentially we're looking, depending on what happens with actions from congress and funding, manufacturers' thinking about developing a whole new wave of COVID-19 vaccines. So lots going on there.

(01:06:31):

And in addition, what we've seen is that over the past few years there's been a collection of submissions of non-COVID vaccines that have been held back that are now all coming along down the pike together. So our vaccines are not in any way, shape or form the routine every day, and the piece that I didn't mention is the piece that's probably most important that I mentioned is that we're using real world

evidence and our surveillance mechanisms for safety and effectiveness of the vaccines that are deployed and now the boosters that are being deployed and just that work on top of our routine surveillance has put a tremendous amount of workload on our biostats and API offices. So it's not over yet from the standpoint of the pandemic in the vaccines arena.

Jeff Allen (01:07:37):

Sara, maybe could I ask you a similar question? Given the influx of products that CDRH had, has there been a degree of regularity in more recent months?

Sara Brenner (01:07:50):

So maybe similar to what Peter described, the division that deals with virology IVD remains underwater, I think, in terms of the volume. There was monkey PPOs on top of that. Now there's Ebola, there's always... Or I shouldn't say always, I think maybe uniquely there've been a deluge of public health events here in quick order. So we've been fortunate and we've hired a lot of new talent so that's helping. But of course it takes a while to fully train and upskill staff to deal with the volume that's needed. So thousands of UA applications and hundreds of UAs issued. And I think that for that division, they're thinking about sustainability in terms of the workload, yes, continuing to up step, yes, but I think it's also time to reset the perspective and consider the reality across the whole office that is not just the virology divisions, but there are a lot of things that unfortunately are killing people and infectious diseases are one of them.

(01:08:57):

So the workload across the whole office, believe it or not, hasn't gone down throughout the pandemic. It's also continued to tick up. So our office has expanded by I think over a hundred and perhaps even more staff, but [inaudible 01:09:15] two IVDs, we've also launched a diagnostics data program with two different arms, one arm focusing on laboratory interoperability for diagnostic data called the SHIELD program, and then a digital diagnostics program focused on the challenges I mentioned earlier for capturing, harmonizing, and transmitting diagnostic testing data from any point of use. So we've got some new initiatives that are springing up and an expansion of scope and staff that's helping to get more hands on deck for us. But I don't think any of us, at least in our tenure here, hope to return to a world of January 2020. Turn it over.

Jeff Allen (01:09:57):

I can certainly say that we, as an American public, certainly thank you for your heroic efforts in the last couple of years for all of you and your colleagues. Maybe one last question as we wrap up here. Thinking back to these collaborative efforts and bringing together oftentimes diverse stakeholders, I'll just ask each of you really quickly, maybe we'll start with you Jacqueline. Looking at some of these lessons learned through the Evidence Accelerator, are there other areas that come to mind? Dr. Caleb alluded to this a little bit. Are there other areas that come to mind where this type of collaborative data sharing could be useful into the future?

Jacqueline Corrigan-Curay (01:10:38):

Certainly. I think we're always interested in these pre-competitive collaborations, which you had in COVID. It was a common problem impacting every sector or society and a really great motivator. So hopefully, as you said, we won't go back to a problem that big anytime soon. But bringing groups together and identifying problems where we can find a space, we're sharing knowledge advances the interest of all parties, and that's a big win for public health. I think the focus has been, as we've come out of the pandemic a little bit and not completely, I would say there's a lot of work still being done, is how do we create an infrastructure of evidence generation that can leverage real world data? We also would like to be able to randomize and get rapid results on the therapeutic side where we really did need a lot of randomized trials so we can provide evidence as quickly as and efficiently as possible.

Jeff Allen (01:11:34):

Great. Thank you. Peter, any thoughts from your perspective on other areas that periodic engagement could be useful here?

Peter Marks (01:11:45):

Yeah. I think that as we're moving along here, I think that there are networks that have formed during this time that could continue along in some form that would allow us then to expand them if necessary for the next wave of something that comes along. And I think it'll be important to keep those networks going in some way because I think there's still a lot of productive work that can come from them that may inform routine care. Again, vaccines are used all the time and constantly evolving recommendations for their use. There probably are things we can do in between pandemic times that would allow us then when we have the next event to scale up and be ready.

Jeff Allen (01:12:56):

Great. Thank you. And Sara, I'll give you the final thoughts here. I know CDRH is involved in many different ongoing collaboratives, but any closing thoughts on how diverse communities and various experts that may not regularly interact with FDA could be helpful in the diagnostic space outside of even infectious diseases?

Sara Brenner (01:13:17):

Yeah, absolutely. One of the big takeaways for me, and I came into federal service after a couple of years previously in EOP and before that 10 years in academia as a tenured faculty member. So coming from the outside in, it was apparent then and now the public doesn't always see what's going on inside of the federal bureaucracy. It's difficult especially to see inside an agency like FDA. And by see, I mean have an understanding of what we do and how we make decisions and how we gain the public's trust through being transparent about our risk benefit analyses and the data that we're using to make different decisions under different circumstances. So I think one of the big takeaways is that this type of engagement has to continue. It's beneficial for the community, for stakeholders, it's beneficial for the agency. I think it's good for the country in terms of public trust.

(01:14:12):

And we all know at this point that there's a lot of ahead with regards to building public trust in public health and public private collaborations to address different challenges. As a public health physician, I think there's a lot to reflect on with regards to what we've all been through in the last several years. And I look forward to doing that with colleagues both in and outside the federal government. And there's a lot of ways to do that here, maybe more than people know at FDA, but this has certainly been an outstanding one of them that's spun off in many different directions that we look forward to continuing the dialogue around. Thanks.

Jeff Allen (01:14:47):

Well, thank you. I thank you for joining us today. Thank you for everything that you are doing day in and day out. I think over the last couple of years, of all the chances I've had to interact with you and your colleagues, I've never seen anyone without energy. So we are extremely appreciative of everything that you continue to do. And I'll turn things over to Susan and again, want to thank the foundation for their leadership as well. Susan?

Susan C. Winckler (01:15:11):

Jeff, thanks so much, and so well said, Sara, Dr. Marks, Dr. [inaudible 01:15:16], just thank you so much for your contributions and it's just an honor to hear from you and work with you. So appreciate that opening panel. And now we'll move to session two. I'll note another component of the COVID-19 Evidence Accelerator was actively collaborating to dig into the real world data about COVID. And our second panel is going to a deep dive into the Evidence Accelerator's research findings and methodologies. So to guide that dive, I'm going to turn the microphone to my brilliant and perpetually funny colleague, Carla Rodriguez-Watson, who heads up the research enterprise at the foundation. Carla, are you ready?

Session Two: Research Findings and Methodologies

Moderated by Carla Rodriguez-Watson, PhD, MPH, Director of Research, FDA Foundation

Nicolle Gatto, PhD, MPH, Aetion, Inc.

Sandy Leonard, MPH, HealthVerity

Vincent Lo Re III, MD, MSCE, University of Pennsylvania

Anand Chokkalingam, PhD, Gilead Sciences

Nancy Lin, ScD, IQVIA

Aloka Chakravarty, PhD, Office of the Commissioner, FDA

Carla Rodriguez-Watson (01:16:00):

We are. Thank you so much Susan, and good afternoon everybody. Welcome to session two. This is where we're going to dig in to discuss research findings and methodology from the COVID-19 Evidence Accelerator. I'm so thoroughly honored and appreciate the opportunity to share the stage with this panel. Each of these very smart people, and that's not just [inaudible 01:16:27], jumped in, buckled up and joined us on our journey over the last two plus years to help the Evidence Accelerator community understand what data about COVID-19 could be generated to produce evidence.

(01:16:43):

They include Dr. Nicolle Gatto, Chief Science Officer at Aetion, Sandy Leonard, Senior Vice President of Partnerships and Real World Data Solutions at Health Verity, Vincent Lo Re, oh, and if you all would turn on your camera so people can see you, who is Associate Professor of Medicine at the University of Pennsylvania Division of Infectious Diseases, Dr. Anand Chokkalingam, Executive Director and Head of Real-World Evidence for Gilead's Virology Therapeutic Area, dr. Nancy Lin, Director of Epidemiology, Real World Solutions at IQVIA, and Dr. Aloka Chakravarty, Director of Data Analytics and Senior Statistical Advisor in the Office of the Commissioner at the United States FDA. Welcome everybody, and thank you.

(01:17:43):

So in session one, you heard about the Evidence Accelerator lab meetings. Here in session two, we are talking about the compliment work stream, the parallel approach to analysis, which later gave way to therapeutics vaccine research questions. Next slide please. The purpose of the parallel approach to analysis was to assemble a community where questions about COVID-19 could be urgently explored through the lens of real world data and real world evidence generation. Next slide please.

(01:18:28):

So our step-by-step approach started with the FDA. The FDA prioritized research questions that you turned to the Evidence Accelerator community to crowdsource their feasibility and their relevance. Next step. Next slide please. In March 2020, we sent around a survey to understand what data were available in two weeks, one month, three to four months to help us understand which questions could be answered most efficiently and to identify common data elements and develop translation tables. Once that was sorted, we quickly got organizations to sign up and contribute to the analysis. Next, please.

(01:19:19):

These accelerators, as we called them, collectively developed common study protocols and statistical analysis plans, which they executed against their native data sets and ran analyses in "parallel". Next step please. Accelerators brought those results to weekly parallel analysis group meetings where we were able to share them side by side and do rapid cycle analysis on methodological issues, findings, which informed our common approaches and an assessment of generalizability of the results across data sets. We summarized trends across those data sets and in many cases published collectively. Lest you think we did post hoc analyses, the common protocols were designed as a stepwise approach where there was a design feasibility assessment first before we embarked on developing the study protocol. Next slide please.

(01:20:29):

And we focused the parallel analysis for each of our distinct work streams in therapeutics and diagnostics. Next slide, please. All the while, we followed these collectively developed principles. Now many of you have seen this before, and if you haven't, please go to evidenceaccelerator.org so you can download them. In summary, what these principles outlay is our north star to do good work, to act fast, and do good work primarily through ruthless transparency. And now I'd like to introduce Dr. Nicolle Gatto, who will share the parallel approach to analysis taken to understand the utilization of hydroxychloroquine with or without azithromycin in hospitalized COVID-19 patients. Nicolle, would you pick up the mic please?

Nicolle Gatto (01:21:26):

Yes, can you hear me?

Carla Rodriguez-Watson (01:21:27):

We sure can.

Nicolle Gatto (01:21:28):

Okay, great. Thanks Carla. We can go to the next slide. So as Carla mentioned, the hydroxychloroquine project was the first parallel analysis that was conceived and conducted by the Evidence Accelerator. And because of that, it was very much process oriented as much as it was focused on getting an answer to a clinical question. So this was the first project. We had seven research groups and a total of nine partners, once we included the data partners as well. We in this piloted the common protocol and also the collaborative, but independent parallel analysis approaches. In six of the data partners were using EMR data and one was using hospital chargemaster with linked claims. And the parallel analysis were intended to be as similar as possible, but did allow for flexibility when needed to allow for differences in the data or any unique limitations to the data sources. Next slide. So overall, using this parallel analysis format, we sought to describe outcomes associated with hydroxychloroquine, with or without azithromycin for hospitalized COVID-19 patients across seven real world data sets in the United States. In these, the specific aims were to characterize the baseline characteristics of the patients that were hospitalized with COVID-19 to characterize treatment patterns of hydroxychloroquine with or without azithromycin, and to describe safety and effectiveness outcomes, either descriptively or in some cases comparatively among these patients looking at those treated and untreated. Next slide.

(01:23:12):

So we set out to use a common design and a common analytic approach, but there were a lot of variations across the data sources and the data partners based on different needs. And the reality is we were moving so fast and this was such early days that some of us were developing our own analytic approach. At the same time, we were working together to try to find common ground. So it was all moving not just as a parallel analysis and common protocol, but moving in parallel.

(01:23:44):

I think some of the common elements, we generally identified patients that were hospitalized with COVID-19 from January to June of 2020. We looked at treatment groups that included HCQ alone, HCQ with or without azithromycin or neither HCQ or azithromycin. We looked at outcomes such as mechanical ventilation and mortality and in some cases, discharge. And we sought to use a common analytic approach to estimate a Cox proportional hazard model. But we all used different methods to get there. Some used inverse probability weighting, some used propensity score models, some used risk set sampling with propensity scores. And there were also differences in how we identified an index state. So some of us identified people who were treated with HCQ at admission or not or some. And some groups looked at HCQ administration within 48 hours of admission or not. And then others of us identified index dates based on when HCQ was administered during the hospitalization with time matched and other matching for finding referend patients. Next slide. So as I said, there were seven partners and nine in total when we add in our data partners. We looked at over 20,000 patients hospitalized with COVID-19.

The partners included Aetion and Health Verity, COTA, Hackensack Meridian Health, Dascena, Health Catalyst, Syapse, TriNetX, and Veteran's Health Administration. We had fairly good coverage across the US with concentration of patients in sites in some areas like California and the Midwest. And across the board, we always compared side by side. We looked at the data itself. We looked at structured versus unstructured fields. We looked at completeness in what was captured and what wasn't. We looked at differences in patient characteristics and then ultimately, in how we were defining algorithms.

(01:25:54):

Just the amount of time spent, I think Amy mentioned earlier that there was a lot of consideration around how to define severity and how to identify and define oxygen therapy, but we had almost as much conversation those early days about how to define COVID-19 itself. So we all did the best we could. We used the data that we had available and then we just tried to clarify when we are using different algorithms. We also compared our study designs. So you're seeing just two examples there where the primary core part of the design was similar, but there were those differences that I mentioned earlier. Next slide.

(01:26:34):

So in terms of the findings, this is looking at just a small sample of the baseline data and the unadjusted risks. Overall, we found that the demographic and clinical characteristics of patients across data sets varied quite a bit, which is not surprising. But overall, trends for treated versus untreated patients within each dataset were more similar than looking across data sets. We also saw that patients that received HCQ and azithromycin were typically older than 45 and more likely to be male. And that prior to adjustment, the risks of mortality and mechanical ventilation were generally higher among those treated with HCQ and azithromycin versus those treated with neither, which would make sense if people with more severe disease were being channeled to those treatments. Next slide.

(01:27:27):

In terms of our primary outcome comparative analysis, we found that confounders were generally well balanced across treatment groups after adjustment, which was great considering that we were trying to adjust for a lot of baseline comorbidities and severity of a disease that was changing day to day. And overall, across the five groups that did run the comparative analyses, there was no clear trend or association between HCQ treatment and mortality or mechanical ventilation. And if anything, there was some indication in some cases of potentially elevated risk with treatment. And in the few of the cases, the confidence intervals excluded the null. But certainly, there was no evidence in these analysis of any benefit and no clear evidence of a harm. So just because this, we can go to the last slide, because this was the first parallel analysis, we had a retro and discussed what we had done and what we might do that we would apply to the future parallel analysis.

(01:28:33):

And I think very much these bits of advice were taken by the other research groups. So we used, as Carla said, a step-wise approach. We looked at sample sizes, the size of the data overall, the sizes of the patient populations. Once we applied some basic inclusion exclusion criteria, we looked at geographic coverage and patient characteristics. And then we really thought about the feasibility of each data source to answer the research question at hand. And in some cases, that meant that some research groups decided not to do all of the comparative analyses or not to look at some of the endpoints, which

seemed really appropriate because we were using that descriptive information to optimally design the subsequent comparative analysis. As noted many times now, we really tried to use uniform definitions and methods were possible, but we allowed variation when we needed to accommodate the data.

(01:29:29):

And I think one of the most important things that came out of this was that the transparency, I think Carla said transparency three or four times. This was really critical. Sharing the analysis plans, sharing our data definitions and our algorithms, the study designs that we were following, having weeks of discussions around how to define time zero, and then ultimately being transparent about not just those differences, but also some of the limitations that we experienced in our own analyses so that all in all, we could interpret the whole body of evidence I think was a major benefit of the work that we did. So Carla, I will turn it back to you.

Carla Rodriguez-Watson (01:30:10):

Thanks so much, Nicolle. Thanks for bringing us back and again, underscoring the importance of transparency and we'll get back to more discussion on exactly how we came to some of these decisions. But right now, I'd like to introduce Dr. Anand Chokkalingam from Gilead, who will discuss with us the parallel approach to analysis for characterizing the use of remdesivir in hospitalized COVID-19 patients. Anand?

Anand Chokkalingam (01:30:39):

Thanks so much, Carla. Thank you also to the Reagan-Udall Foundation friends for their leadership during this time and for bringing this all together. I got involved with this fairly early on. I've been leading a lot of Gilead's efforts in real world evidence for characterizing the potential effectiveness of remdesivir from the start of the pandemic. And it's really a pleasure to be able to, and fairly humbling, it took to be able to speak on behalf of this massive group of engaged and energetic scientists trying to get a better understanding of what would be effective in the early days of the pandemic. So I'm presenting the work of a team I think is as obvious here. So before I dive right into what our aims were, I think it's important to just keep a couple of things in mind. Remdesivir was granted EUA in May of 2020. It's a little bit different from hydroxychloroquine.

(01:31:38):

It's applied in the hospital. It's usage was brand new. There were not yet codes for it to assist and to enable analysis and real world evidence. And one other piece to keep in mind is that is early supply was still somewhat limited. The other piece that to keep in mind was that our measures of effectiveness were in evolution. We first talked... I don't know if some will remember are seven to eight point scale of clinical improvement, which came out of the NI ACT one trial.

(01:32:13):

And so these things all came to our head for us as we put together that this parallel set of aims for the parallel analysis. So the first aim was obviously to characterize the use of remdesivir in hospitalized patients after implementation of the EUA, to develop and construct propensity score models, and then to assess whether those models were actually going to be able to achieve the kind of balance that we needed to. And the final aim, which I'll talk about a little bit today, is assessing the risk for acute kidney

injury, ventilation, discharge in hospital mortality, and length of stay amongst hospitalized COVID-19 patients treated with their own remdesivir versus untreated patients. Can we go to the next slide please?

(01:32:59):

So there were many, many partners here. There were partners who were data stewards. There were partners who were representing all parts of the data ecosystem or the healthcare ecosystem, including not only the folks here, but of course methodologists and clinical people who helped us understand how to translate and operationalize a lot of the variables that were sitting in these data sets. These folks brought incredible energy and just look at this enthusiasm and willingness to collaborate. And I think one of the things here to keep in mind is that they represent many different data set types. We have data sets ranging from EMR and administrative claims data to hospitals charge master data, and as well as some chart reviews that were conducted ad hoc. So that's really important to keep in mind. So on this slide here, you see that we have a study design that was arrived at. And the first phase was of course to focus on the hospitalization period as remdesivir is administered in the hospital.

(01:34:06):

And to look at which patient population are we going to focus on? We would focus on patients who were not invasively, mechanically ventilated or on ECMO, and then all sorts of various windows in place to help us measure different covariance. Now, one of the things that I'll mention is that all of the partners on the previous slide, many of them were working on, as Nicolle said, each group's own analyses and were in parallel working with the parallel analysis through the Evidence Accelerator. And that's important to bear in mind because what did end up happening here is we needed to be able to thread the needle between the idealized set of approaches that might work for any given data set and finding some common denominator that would work for the group. And that was, it's certainly one learning for us, but that this was our study schematic and we're looking for all of our different outcomes in this window here. Next slide please.

(01:35:10):

So we are working right now to synthesize and explain some of the results that we see across studies. So what I'm going to focus on today, rather than individual numerical results, is a set of the learnings that we've actually identified here. I'm going right to these because I think there are a few things that have come up that are really critical that I think we learned from this. The first all, it's something that is common to real world evidence in epidemiology in general, is making sure what all of your key covariance are. And so I think here, we really found that variables like COVID-19 disease severity, to name one, is very, very important to be able to capture and address in our analysis, both individually and parallel. Other pieces that I will say were really helpful to discuss and to bring to bear are how.

Ananda Chokkalingam (01:36:03):

... To discuss and to bring to bear are, how to address methodological considerations such as immortal time bias and channeling bias that were especially acute at the time of, the start of the pandemic. Here it's, I mentioned this because the window in which Remdesivir is used is a narrow window in the time of hospitalization, and many of us in the real world evidence space have really worked across longer time

scales than a week, two weeks, three weeks or four weeks. So, and to be able to capture that change of what the severity at baseline symptoms at prior, that was very, very challenging indeed.

(01:36:38):

Other piece to keep in mind, which is sort of related, is the importance of common operational definitions of medications, both for the exposure I mentioned before, that we didn't actually have codes for Remdesivir in it's earliest days, as well as co-variants like [inaudible 01:36:55] and some of the comorbidities, and finally, I think as I mentioned here, this challenge of examining this narrow window of exposure and the subsequent outcomes in that narrow space of time were, definitely posed some interesting challenges for the group, but it was an incredible amount of work and effort that went into identifying some of the areas and challenges that we experienced, and we are working together to synthesize the results today.

Carla Rodriguez-Watson (01:37:23):

Thank you so much Anand, and thank you for reviewing these high level learnings, which really was the jewel of what came out of this parallel analysis. I want to turn now to Dr. Vin Lo Re from the University of Pennsylvania, who's going to share with us the experience of the coagulant, the work group as they sought to understand the risk of coagulopathy in hospitalized COVID-19 compared to influenza. Vin?

Vincent Lo Re III (01:37:58):

Carla, thank you. Can I have the next slide please? So we heard from Dr. Corrigan Kari about the interest of the agency in examining COVID related coagulopathy, and this parallel analysis group was really focused on evaluating the 90 day absolute risk of arterial thromboembolism, acute myocardial infarction or ischemic stroke, which I've designated as ARE, and venous thromboembolism defined as acute DVT or acute deep venous thrombosis or pulmonary embolism, which I've abbreviated as VTE, in two groups of individuals. Patients initially diagnosed with COVID-19 in the hospital between April, 2020 and May, 2021, and compared that group to patients initially diagnosed with influenza in the hospital from the 2018 to 2019 flu season. And the reason that we focused on influenza as the comparator, is that it's another respiratory virus, it's been associated with pandemics, and influenza has been associated with both acute myocardial infarction and stroke, as well as venous thrombolic events. Next slide please.

(01:39:19):

So, as with the other parallel analyses, there were a number of partners for this within this group. Datavant, Symphony Health, HealthPals, Veradigm, the FDA Sentinel, of which I was a part of, and Syapse. And there was a host of different data that obviously varied by the partner. Both Sentinel and HealthPals were consisting of data that included electronic health records and claims. Datavant included claims data from retail pharmacy in remittances, and Syapse was an exclusively oncologic electronic health record that included data on linked mortality and SEER cancer data. Next slide.

(01:40:08):

Similar to what Dr. Gato had mentioned in her talk, the group generally used a similar approach but maintained some flexibility given the differences in data. And this common analytic approach is schematically shown on this slide. You'll see at the bottom that our index date, the date of start of follow up was the date of hospital admission for either COVID-19 or with influenza. And we had various

look back periods to ascertain baseline comorbidities, medication exposures, and laboratory results, and patients were followed from the date of hospital admission through one of the arterial or venous thromboembolic events, death, dis-enrollment, 90 days after the index date, since our goal was to evaluate 90 day absolute risk rate, or the end of study data, whichever came first. And if you'll just advance please and our... Just next slide, please.

(01:41:14):

And our groups calculated the 90 day absolute risk and incidence rate of arterial and venous thrombotic events, and utilized propensity scores to determine hazard ratios of each of these outcomes in persons with COVID versus influenza. Next slide please. So the first date I'm going to show from our parallel analysis results are from HealthPals, Veradigm, and you'll see at the top of the slide is the overall numbers of persons hospitalized with COVID-19 and influenza. The curve at left focuses on arterial thromboembolic events and at right, venous thromboembolic events. The Y axis shows the cumulative rate of each of these events and the X axis is the days since index date. The blue curve represents the patients hospitalized with COVID-19, and the green curves, patients hospitalized with influenza. Focusing on the curve that left, you'll see that there really was in this analysis from HealthPals, no increased rate of arterial thromboembolic events in patients with COVID-19 compared to influenza, and the hazard ratio was 1.02 was non significant. At right however, the analysis revealed a significantly higher rate of venous thromboembolic events in patients with COVID versus flu. The hazard ratio was 51.53 and this was significant, indicating a 53% higher rate of venous thrombolic events in patients hospitalized with COVID versus influenza.

(01:42:51):

Next slide please. The next data I wanted to show from the parallel analysis from the FDA Sentinel Group of which I was part, and this table shows the relative hazards for 90 day arterial thrombolic events among patients hospitalized with COVID and flu. And what we did a little bit different from the other groups was we stratified the results based on time period. So there was a time period 1 for COVID-19 that extended from April 1st, 2020 to November 30th, 2020. That was a period when there was no COVID-19 vaccine available. And the second period extended from December 1st, 2020 to May 31st, 2021, when COVID-19 vaccines were available in the US, and if you could just go to the next slide please.

(01:43:38):

Looking at the hazard ratios of arterial thrombotic events in persons with COVID-19 versus flu, similar to what was observed overall in HealthPals in either period 1 or COVID-19 period 2, there was no significantly increased rate of arterial thrombotic events in persons with COVID versus flu. In contrast, if you go to the next slide, please. When we looked at individuals... Next slide please, who had an inpatient arterial thrombotic event and evaluated all-cause 30 day mortality, we found that patients with COVID-19 had a more than three full higher rate of mortality within 30 days compared to those with influenza, both in one and in two.

(01:44:25):

Next slide please. And this next slide, next slide please, shows the hazard ratios for 90 day venous thromboembolic events among patients hospitalized with COVID versus flu, and again, stratified by period 1 versus period 2, and if you'll just go to the next slide, you'll see that similar to what was found overall in HealthPals was that the rate of venous thromboembolism was significantly higher, both in

period 1 and in period 2, compared to persons with influenza. The hazard ratio in period 1 was 1.6, the hazard ratio in period 2 was 1.89 and these were significant, 95% competence intervals did not cross 1. Next slide please.

(01:45:13):

And similar to what we found in the arterial thrombotic event analyses, among those with inpatient VTE events, the rate of all-cause mortality within 30 days was 2.96 higher for COVID-19 versus influenza in period 1 and 3.8 fold higher for persons with COVID-19 versus influenza in period 2. Next slide please. Looking at the results from Datavant... Oh, yep. Next slide. Looking at the results from Datavant, and focusing at right for the site and PS... Propensity score matched hazard ratios, there was no increased rate of arterial thrombotic events in patients with COVID versus flu. In this analysis, the hazard ratio was 1.10 was non significant, 95% confidence intervals crossed 1, but in contrast to the two prior groups, Sentinel and HealthPals, this analysis showed no increased rate of venous thrombolic events in patients with COVID versus flu. The hazard ratio was actually 0.74, but the confidence intervals were quite wide, 0.21 to 2.67 crossing 1. And then next slide.

(01:46:32):

The last group was Syapse. Again, this was the data that included persons with cancer. This table shows the absolute risk in incidence rates for persons hospitalized with COVID-19 and with influenza at right, and at top for those arterial thrombotic events and at bottom, venous thromboembolism. And you'll see just focusing on the bottom that among persons with cancer in these data, the rates of venous thromboembolism were significantly higher in persons with COVID-19 versus influenza, and you'll see that the absolute risk was 3% in COVID-19, 1.5% for influenza.

(01:47:15):

But there was, similar to HealthPals and Sentinel, there was no increased rate of arterial thromboembolism in persons with COVID versus influenza. So to the next slide please. So this parallel analysis used different data sources, including one that was specific to persons with cancer to address the primary studying, and three of the four partners observed quite similar findings, an increased 90 day risk of venous thromboembolism in patients hospitalized with COVID versus influenza, but no increased 90 day risk of arterial thromboembolism in COVID versus influenza. And just last slide please. And I think one of the things that Dr. Abernathy had mentioned is the importance of bringing together a disparate group like this, all focusing on a common goal and making sure that we disseminate these findings. And our group from Sentinel published our results in JAMA in August, and the group from HealthPals published their results in Plos One in January, so I think shows the power of bringing together these groups. So I want to thank you for your attention, and Carla, back to you.

Carla Rodriguez-Watson (01:48:30):

Thank you so much, Vin. And now last but not least, I want to bring Dr. Nancy Lynn to the stage to talk about how the diagnostics work group leveraged the parallel approach to analysis to characterize the utilization and performance of COVID-19 serology tests. Nancy?

Nancy Lin (01:48:54):

Thanks so much. Carla. Can you hear me?

Carla Rodriguez-Watson (01:48:57):

Yes, we can.

Nancy Lin (01:48:58):

Okay. Great. Good afternoon everyone. As Carla mentioned, I'm Nancy Lynn, director of Epidemiology in the Real World Solutions Business at IQVIA. Prior to joining IQVIA, I served as a senior oversight role for the team at Health Catalyst, one of the research partners participating in the evidence accelerator parallel analysis so, it's a pleasure and an honor to join the panel today to be able to share findings from the diagnostic parallel analysis on behalf of a very large team of partners, and of course appreciate the leadership and energy of Reagan-Udall Foundation and Friends of Cancer research. So next slide up. So I think, in the first session we heard from Dr. Burner from CDRH about the need and also the challenges inherent in assessing world performance of diagnostic tests. The diagnostics parallel analysis group was formed specifically to address questions around utilization and role performance of SARS-coV-2 serology tests, as Carla mentioned.

(01:50:04):

This study had two research aims. One which was to describe the serologic testing by demographic, geographic location, baseline clinical presentation, team comorbidities. Part of this aim included an extensive assessment and characterization of the data that would be available to support real evidence generation around the performance of serologic tests. So really, aim one, we can imagine is really a means to understand the current state of interoperability at the time that the study was initiated. And by interoperability, I mean interoperability across instrument, lab and clinical data. The second aim was to estimate the positive set agreement of serologic tests among patients with positive SARS-coV-2 by molecular assay and to identify factors associated with the seropositivity. Next slide please.

(01:51:08):

There were six partners that participated in a diagnostics parallel analysis, and they're listed on this slide. What you'll see similar to the other parallel analyses are that, the partners represent a mix of real world data types, including claims data, charge master and EHR data, and they're contributed from a variety of sources, including partners pulling data from a large US payer, data coming from partners that were data aggregators or large networks, as well as partners that are a single healthcare delivery system. And so the data used in the study covered the same time period for the most part. For five of the six partners, the study period was from March, 2020 to December, 2020, and for one of the partners there was a slightly larger window covering March, 2020 through April, 2021. So really the focus at this point was on the early phases of the pandemic. Next slide please.

(01:52:20):

Again, similar to the other parallel analysis, the diagnostics parallel analysis group adopted a common design and analytic approach, starting from the premise of trying to maintain as much similarity as possible, but understanding that flexibility was needed and customization might be needed depending on the composition and what might be available in the data sources of each of the partners. So, generally speaking, eligible patients included individuals who tested positive for SARS-coV RNA by molecular tests between March and September of 2020, except for the one partner that allowed [inaudible 01:53:03] accrual through April, 2021. And for these patients, the date of the RNA positive

tests served as the index or cohort entry date. And I'll link a note here under that. The data code entry is actually one of the elements where customization was needed, in that date of laboratory testing or dates of laboratory testing come in different varieties and are available in different ways across the partners.

(01:53:35):

Some partners might have had data of the specimen collection, others might have had data of the result. And so what we learned following that characterization of the data source itself was that, what might work best for this parallel analysis was to use a hierarchical approach, where the data specimen collection was considered the primary selected element when it was available, followed by the data session, and then lastly, by the date of result for setting an index state for each patient. Additional eligibility criteria were applied to minimize potential differences in missing this across the partners. As I mentioned, the partners included partners with closed claims data. Other partners were EHR based, partners within healthcare delivery networks. And so there are certain assumptions around observability of certain data elements within each of those types of data sources. So across all partners, we required all patients to have a clinical encounter within two weeks of the index state, and this was applied to increase the likelihood of capture of documented presenting symptoms. However, again, as a customization of the protocol, for our claims data sources, patients were additionally required to have at least six months of enrollment in the year prior to the index state. Patients were then followed through 90 days for the occurrence of serologic testing, and then for patients that were included in cohort, baseline co-variants were ascertained within defined windows before or on the cohort entry date, as noted in the schematic.

(01:55:29):

Descriptive statistics were performed to describe utilization of the serologic tests by pre-specified baseline characteristics. And then for the second aim, among patients with a positive RNA who also had a serological test result within 14 to 90 days following the positive RNA, we calculated positive person agreement. And finally, we estimated buzz ratios for zero positivity by selected baseline characteristics. Next slide please. So the next several slides are just highlighted learnings from aim one and aim two, but in terms of learnings related to both our understanding of the rural data that's available as well as learnings from the scientific analysis. In total, over 930,000 individuals were identified across the six partners as having positive RNA for SARS-coV-2, and of these 4% were serotested within 90 days. 15% of those serotested within 90 days actually had testing occur within 14 days from the RNA positive test. And the highest occurrence observed for serotesting was actually serotesting on the same day as the RNA positive test. And so this close temporal proximity of positive PCR tests and serotesting was somewhat unexpected, but based on investigations by the local partners and here I just would like to highlight the importance of having an understanding of the local context.

(01:57:04):

What appears to be driving at least some of this skew in the distribution, is the implementation of policies within health systems to screen patients, or have pre-procedure screening of patients for active or past SARs-coV-2 to evaluate the risk of [inaudible 01:57:24] infections, and so this was part of the characterization that was done that helped inform and determine our time interval and justification of our time interval of interest for when we were thinking about the occurrence of serologic tests relative to RNA tests, and what tests pairs would be eligible for an assessment of positive predictive value, not

positive, present agreement. Next slide please. So, when assessing their serotesting by various baseline characteristics, we found that even in a population of patients with active infection, race and ethnicity data were largely missing. What we mean by that I mean greater than 30% were not available at all in some of the data sets. In addition, we also, if you look at the bottom of the slide, what we found during our characterization phase was that there was a large amount of missing this on information on manufacture serologic testing among those that were serotested where this data was largely or completely missing for three partners, missing for about a quarter of patients in two partners, and only in one partner, partner five was that complete data available on manufacturers serologic testing. And this was very important for our group to understand, to help inform which partners or what analyses might be possible given the real data that we had within our networks. Next slide please.

(01:59:16):

And just one more click. Next slide please. And this is really just a graphic that is probably very familiar to those who attend a COVID-19 evidence accelerated calls, which is all to say, knowing that there is a highly distributed landscape of diagnostic testing, there's a complex flow of data from instrument to lab and to clinical data in VHR. One of our main findings is that the largeness of manufacturers serologic testing really points to a lack of data interoperability that has limited our ability to completely describe use of products as well as assessments of their safety effectiveness performance in the real world. Next slide please.

(02:00:09):

Just a couple of highlighted results from the second aim. Not to beleaguer a lot of information that's on the slide, but we did find the odds ratios for seropositivity were numerically higher for Hispanics compared to non-Hispanics, as well as for patients with diabetes versus without, and for patients with obesity, whereas ratios for seropositivity were lower among those with immuno compromising autoimmune conditions compared to those without those conditions. Next slide please. Similarly, we did see a higher positive percent agreement among patients who are Hispanic compared to non-Hispanic patients, and among patients who were presented with at least one COVID related symptom compared to those with no symptoms. And so, I'll stop here knowing that we have, well, we should have time for additional discussion, but again, just some learnings from the diagnostics parallel analysis as it relates to real world data. Our assessment of serotesting, I was able to capture a large cohort of patients across the US from diverse data sets that leveraged VHR and our claims data.

(02:01:28):

However, the extensive characterization of data had highlighted that there are substantial missing data elements as it relates to specific questions of interest, including those related to specific manufacturers serologic tests. But I think that, as with all of the parallel analyses that have presented today, there is tremendous value in the stepwise approach that was undertaken in each group to first characterize the data, to understand and document the data source, data messiness, document the operationalization of different definitions across the printers, so that we could support both appropriate analyses and interpretation of results. And I'll turn it over to you, Carla.

Carla Rodriguez-Watson (02:02:20):

Thank you so much, Nancy. So I think what you described and what we saw from all the presenters was really, a lot of heterogeneity. From claims or EHR only data sets to linked claims in EHR, from single systems to networks and so much more. I think what was salient in the projects presented here was a very clear articulation of what the conceptual question was, and what you all worked out was the operationalization of that question. You made some joint decisions about what you would align on, what was a must have and where there could be a plan deviation. So what were some of the most salient methodological or data issues that you saw arise? And what was an important lesson learned about how your group drove towards that common protocol?

(02:03:20):

I'd like to kick off the discussion with Nicole. Nicole, would you unmute and talk to us a little bit about some of the heterogeneity that you observed, and some of those solutions a little bit deeper? I mean, I think everybody commented on that time zero, and thankfully we have graphical designs, study design tools that we use throughout all the parallel analysis so, give it up for Sebastian [inaudible 02:03:48]. And to you. Nicolle?

Nicolle Gatto (02:03:51):

Sure. Thanks Carla. Yeah, that is obviously the first one that comes to mind, and really it's not just because we want to all have the same time zero, but it was more around making sure that we are all avoiding immortal time bias, really creating immortal time bias in our studies. So I think that was worth all of the discussion. And, after a lot of discussion, people I think just did the best that they could with the data and the team that they had available, and if we were doing this now, I think we would work together to find an exact common design, at least identifying what index date looks like and how you pick your referent group. But we were, when I think back to how early that was and how much we were all scrambling trying to catch our breath probably at home and at work, and with all of this really important work, I think what we did was amazing.

(02:04:52):

So it's not a criticism. It's just we'd probably do it differently now than we did, and I think we see that as we look at the other parallel analyses that were conducted after. So, the other thing that comes to mind for me, and then I'll let others jump in here. In terms of data differences, because we were looking at a hospitalized population, some of the data sources had outpatient medications, and that meant that we were able to look at comorbidities and medications prior to hospitalization, and others did not and could only look at baseline characteristics of patients at admission or after. And likewise, some of the data sources allowed us to look at patient outcomes after discharge and others did not. We were only able to follow up to discharge. So, I think we also used those data the best that we could, and it was all complimentary when you put it all together as a package.

Carla Rodriguez-Watson (02:05:50):

Thanks Nicole. So a lot of understanding that transparency helping us and the agency understand who has access to what kinds of data, and maybe how to identify the appropriate data sources for future analysis. Sandy, anything else to add being a partner to Aetion in this hydroxychloroquine question?

Sandy Leonard (02:06:14):

Yeah, yeah. Definitely. I think a couple of the learnings that I think we all came away with, and it was great even as we were preparing for this, was how collaborative, not just between HealthVerity and Aetion and answering our piece of the puzzle there, but across all of the different participants, we were all learning, and we were all trying to figure out how to do this, and so we had to rely upon one another. So crossing those established silos of organization and types of organizations to actually address some of these issues, so understanding, well, "How are you finding this in your data? And what does this look like and where is this code?" I think it was a really helpful way for us, kind of the storming through to get to some of this information more quickly. So that collaboration, I think has been really key.

(02:07:07):

The other piece I think, and Nancy touched upon it a bit, especially for the diagnostics, was being able to get and go back to the source of the data when things were unclear. So, each of the different accelerator partners had different access to different types of data, and so as we're doing the analysis, trying to understand what we were seeing and how might we find some of these elements that might not typically be available in just your typical real world data capability. So I think those two things were really important. That collaboration across, and then being able to work very closely and get back to really the genesis of where that data is coming from.

Carla Rodriguez-Watson (02:07:53):

I just muted my myself.

Sandy Leonard (02:07:55):

You're muted.

Carla Rodriguez-Watson (02:07:55):

Thank you so much Sandy. And since she pointed to you, Nancy, diagnostics really was a different kind of animal...

Carla Rodriguez-Watson (02:08:03):

See, diagnostics really was a different kind of animal. How do you think this heterogeneity influenced our approach in the diagnostics parallel analysis?

Nancy Lin (02:08:13):

So I'll say, that I think we had a benefit of learning from the parallel analyses that started before us, but in terms of being able to think through similar first principles of making sure that we have an extensive characterization of the data source, but also the data elements that are key for particular research questions. And when I think about characterization of data elements, I think about both availability, completeness but also the format in which they're in and the prominence, as Sandy had mentioned. I think as with all accelerators, we were moving really fast. And in some of, I think, the differences across partners in terms of thinking about the access to the data, but also thinking about the journey of the data from source to what's ultimately available in the data source, I think is something that we were all

trying to learn. And it was useful to have that extended phase of almost feasibility characterization to help refine the protocol.

(02:09:19):

So I think when we think about data flow, it's whether the data is actually captured, whether the data is flowing, is transmitted, whether the data is actually stored when received, but also over time, how that format of that data might have changed or been lost, in terms of its granularity across the systems that it travels through. And I think that's something that we were continuing to learn through the diagnostics process. I'll say just examples of that included the variations and testings that might be available. Often they were free text, unstructured fields that some of the partners had, whereas others might have had more structured information that might have been available, related to integration of systems that might be available to them. But all in all, I think this, Sandy and Nicole and others have mentioned, the opportunity to be able to discuss that [inaudible 02:10:31] open way across the partners in a lab environment, I thought was extremely helpful.

Carla Rodriguez-Watson (02:10:37):

Thank you Nancy. And now turning to Aloka, sitting from your regulatory perch and having observed and participated in multiple parallel analysis groups, how does this work inform the work of the FDA?

Aloka Chakravarty (02:10:55):

Thanks, Carla. Before getting to the results, let me touch upon the process that added as much to the learning. The research questions were developed with the accelerators with multiple data sources, EHR claims network, the standalone, so that the research questions could be answered simultaneously. This helped in establishing the process and the [inaudible 02:11:28] for creating common data elements and interoperability. Key important activity that we did, early on, was to look at the characterization of natural history and it helped understand the test performance, identifying treatment, predicting immunity, detecting potential for future waves of infection and tracking mutation. The initial activities helped in rapidly devising the set of core data elements, identifying those that are critical and establishing uniform collection parameters. So our data elements were extracted and how they were being defined really helped in that understanding. The repeating analysis and parallel, by using different analytical tools, have helped understand the findings and the learnings. Further, it helped in validating the role of RWE as a tool for rapidly learning about patient characteristics, treatment patterns, outcome associated management strategies, and they all added to the learning and augmenting what we are learning in the clinical trials, as well as to the [inaudible 02:13:01].

Carla Rodriguez-Watson (02:13:06):

Thanks so much, Aloka. I think towards that totality of evidence, I think Anond, Vin, you both noted, as did Nancy and Nicole and Sandy, "That heterogeneity wasn't just in the data sources, it was in what's happening over time." So this was a rapidly evolving novel disease, where that did not have a ICD 10 code at first, that did not have an NDC code for Remdesivir. And so you had these groups coming together to identify, "Well, how are you defining this? What's the algorithm for COVID-19? How are you identifying exposure to the medication," all these things. So for you, what did that spark for you in terms of learning how to do this work and some of those additional challenges that came up?

Anand Chokkalingam (02:14:06):

I mean, I got something fairly high-level to say there, and I've got to say, that sitting where I sit in a pharma company, I think one of the things I've appreciated most about the Evidence Accelerator was the safe space for us all. We're in a heavily regulated industry. Our hands are sort of bound in a way that maybe many other players don't have. And so what I appreciated in the moment, especially as, we, as a scientific community needed to move quickly, was being able to collaborate and bring every bit of information that we had from our Remdesivir development that the community had regarding every other aspect that was there to bear on this question. So I found that just in incredibly, incredibly helpful.

Carla Rodriguez-Watson (02:14:50):

Vin, anything else to add?

Vincent Lo Re III (02:14:55):

Yeah. I would say just from the standpoint of early on coming at the coagulopathy question, we heard early on in the last session from Peter Mark, that there was really questions from case series, small local regional settings, but there really were no comparators. And I think one of the values of the evidence accelerator, early on, was deciding, "Should we compare patients hospitalized with COVID-19 to another group? And if so, what should that group be?" We had lots of vigorous discussions about, "Should we compare to influenza, should we compare it to other cohorts? And what were the sort of strengths and limitations?"

(02:15:43):

And we recognized there was no necessarily ideal approach, but we thought that with the, I think, infrastructure of the Evidence Accelerator helped us to get to a good comparison. I think the other thing we had a lot of discussion on was just the best approaches to evaluate the outcomes of, "What should arterial and venous thrombotic events be defined as? Should they be hospitalized only?" We recognized that from a hematological standpoint, that there were some folks who were diagnosed in outpatient emergency department settings. And coming up with secondary endpoints that included such settings, I think added value, added benefit to the robustness of our results. So Carla, those are just some of the things.

Carla Rodriguez-Watson (02:16:36):

Thank you for that. And I think what you've all said, is that going back to our principle again of transparency is like, in a lot of these research studies where they're done behind the academic doors and then published, there's not this level of engagement across researchers in different camps. And we all know even within your own institution, there could be one camp that does the same type of research as another camp. And having this discussion to really understand, like you said, Vin, "How do you define arterial or venous thrombosis?" There is not just one way to skin this cat and to be transparent about what that definition is so that these results can be taken into proper context. I think, as Nancy mentioned, in the space of defining a hierarchical approach to Index State really helps us to be able to put those results in context.

(02:17:31):

And when we looked in parallel to see that, and I think all you did, all of you also saw, that in general, these results tended to go towards the same conclusion. However, there were some differences. And when you understand how that played out, whether it was from... It sometimes, at least what I saw, was that it is playing out in terms of the types of data sources really gave us a rich understanding of the trends that were associated with one source versus another. And again, helps to put those results into context. So we covered a lot of ground here and our parallel analysis really generated results about COVID-19. But even more importantly, we learned some lessons about real-world data and how to work together. So I want to thank my colleagues for sharing their perspective during the two plus years that we work together and here today with you all.

(02:18:39):

So please go to the evidenceaccelerator.org to experience the COVID-19 real-world-evidence Primer, which is a collaboration with the International Society for Pharmaco Epidemiology. You can also download it. This real-world-evidence Primer is where we've condensed all of our lessons learned, into what we hope is an introductory level primer on core pharmaco epidemiologic methods for real-world evidence study contact. So these are where all of our speakers today have contributed to outlining for the world. Really, it's free. It's free. Just some of these high-level, important study design features. And if we go to the next slide, please. Nancy talked about missing data. And one of the things that came out of our parallel analysis was a huge amount of missing race and ethnicity information, which really limits our ability to describe real-world performance of medical products. So to hear more about how we are leveraging an accelerator approach to bring together experts from across the healthcare ecosystem, to brainstorm solutions to improve the capture, retention, and curation of race and ethnicity data, please copy and paste that URL onto your web browser and learn more about our real-world accelerator to evolve the standard of care and engagement in clinical studies for communities of color. And sign up, be part of the conversation. Thank you.

Session Three: How COVID-19 and the Evidence Accelerator Have Shaped the Use of Real-World Data

Moderated by Susan C. Winckler, RPh, Esq., CEO, FDA Foundation

Nancy Dreyer, PhD, MPH, IQVIA

Adrian Hernandez, MD, MHS, Duke University of School of Medicine

Harvey Kaufman, MD, Quest Diagnostics

Nilay Shah, PhD, Delta Airlines

Susan C. Winckler (02:20:22):

Carla, thank you so much to you and your colleague panelists for taking us through two years of research in 47 minutes. Always impressive and just great learnings and really appreciate everyone's contributions throughout the time and then speaking today. So I'm going to take us to our third panel as we round the corner and think about things as we're moving forward. So we want to turn now to our use and understanding of real-world data and how that's been shaped by COVID-19 and by the work of the Evidence Accelerator. So joining me for this conversation, we've gathered four, real- world data gurus. Now that's my label for them. It's not on their business cards. But joining for the conversation is

Dr. Nancy Dreyer, who's Chief Scientific Officer Emerita for IQVIA real-world solutions and an Adjunct Professor of Epidemiology, at the University of North Carolina at Chapel Hill.

(02:21:23):

We're going to provide a little bit of competition from another portion of research triangle and bring up here Dr. Adrian Hernandez, who's the Executive Director of the Duke Clinical Research Institute, Vice Dean of the Duke University School of Medicine and a member of the Foundations Board of Directors. Bringing us the regulated industry perspective, we have Dr. Harvey Kaufman, Senior Medical Director in the office of the Chief Medical Officer at Quest Diagnostics. And rounding out our discussion with potentially unusual stakeholder for the FDA community, we have Dr. Nilay Shah, Managing Director of Health Analytics and Innovation at Delta Airlines.

(02:22:02):

So let's jump into our conversation here. If I could have all of my panelists with their cameras on. I'm going to turn first, Harvey, it's great to see you, like I've seen you on nearly every Evidence Accelerator meeting. But want to turn to you from your seat at Quest. You were part of an extraordinary amount of testing, that yielded even greater amount of what we might think of as typical real-world data. Tell us about that experience and how you might look at real-world data and evidence differently in 2022, than you did early in 2020.

Harvey Kaufman (02:22:43):

Thank you, Susan and Dr. Amy Abernathy and Amar and the friends of the FDA who made the FDA diagnostic accelerator calls possible and a highlight of my pandemic time as we heard from experts and shared ideas. If the fastest two minutes in sports are horse races, the fastest hour in healthcare were these calls. Quest Diagnostics began SARS COVID 2 molecular testing in March 9th, of 2020. Quest Diagnostics, along with LabCorp provided a vital clinical services laboratory testing for hospitals and physicians across the country. But soon hospitals and others began introducing their own molecular test. And that data challenge emerged, which is how do you aggregate all this data? And although Departments of Health reported this aggregated data and it was part of the New York Times and the John Hopkins site and others, they could never grasp the complexities of the different tests and the different method systems.

(02:23:40):

Further, many hospitals started testing all their inpatients, all their staff, the nursing homes, long-term care facilities, tested the residents and their staff, and that changed over time. There were stark differences that emerged, based on state and regional differences. This changing dynamic of who is tested when and where, the analysis of these specific data spaces subject to these changing dynamics. And it was exacerbated further when there was insufficient testing. I think it was the summer of 2020 and only selected patients were tested. And then, you had introduced them to vaccines. We didn't know who was vaccinated, who wasn't vaccinated. We had new variants and then the rapid antigen test that swept across the country. So that was sort of like the population issue.

(02:24:28):

And then, we have the proliferation of tests with different probes and performance characteristics that were introduced over time and among laboratories that made interpretation challenging. And then PCR

tests with cycle times couldn't be compared. Now Susan, you continually sought for solution such as Project Shield, which just to harmonize test reporting. We need such effort. There's essential for all testing if we're to analyze data across all clinical laboratories, to better understand emerging infections more broadly, acute and chronic health conditions and tests. So what we're left with were numerous observational, real-world data studies that differed greatly based on who was tested when and who was vaccinated when and infected, and the confounding factors of risk factors so we don't have an effective system.

(02:25:17):

What we do have is enormous energy and creativity of many separate people and organizations that culled their own data, but the systematic approach, the free enterprise approach led to a patchwork, although of valuable solutions and observations. The FDA diagnostic accelerator was effective at bringing key leaders together to hear from each other, to collaborate, to propagate great ideas in a safe space. And the unique pace of biweekly and then monthly was critical, but more work is needed if we're going to evolve to an effective healthcare system where we can really look at data and real-world data that can respond to the next emerging infection or pandemic.

(02:26:04):

So I led in many publications and interviews and webinars and publications on pooling, let's see, on the role of serology, the impact of vitamin D, blood groups, drug misuse, notable several gaps in care, in terms of chlamydia and gonorrhea and hepatitis C and drug misuse. I think we're working on our fifth study on gaps in care and cancer diagnoses, blood pressure control, all fun and good. Everyone has to go see their doctor if you haven't already. But we had to have extreme care in interpreting all this data because of the patient selection biases so that they wouldn't impact our studies.

(02:26:46):

One ongoing study of interest is to better understand the role of SARS COVID 2 spike targeted serology, especially in immunocompromised population, interesting study, it's a collaboration with LabCorp. So to answer your question, Susan, Quest Diagnostics performed more than 67 million molecular tests, more than eight and a half million serology tests since the beginning of the pandemic. Starting in May of 2020, we, along with LabCorp, have been providing remnant specimen testing for the CDC to look at [inaudible 02:27:19] positivity prevalence in the US. The first study of that was based on March through July, of 2020, and it showed that 6 to 24 times more infections were estimated per site with [inaudible 02:27:32] prevalence data than with case report data. If you wanted to know the power of real-world data, that's it. This is all in the prevaccination period.

(02:27:41):

Another CDC collaboration is genotyping. We've contributed to the Spheres Project since inception. You can go to CDC COVID data tracking, tracker there are variant proportions to get that weekly update. So in closing, we shared a lot of de-identified data daily with the CDC, weekends, holidays included and others in government, identifiable data to public health agencies. We published lots of studies presented in many forums, but the pandemic has opened up large wounds on our healthcare system and the clinical laboratory network. The FDA diagnostic accelerator shined a bright light on that wound and what, despite that, have accomplished. It's my hope that these lively presentations and discussions will lead to a better systems that'll provide solutions that will improve our healthcare.

Susan C. Winckler (02:28:33):

Harvey, thank you. I'm thinking about the 67 million tests and the data generator from two pieces. We know there were many, many more, and then even as we were just hearing from Dr. Brenner earlier in the session about all now the over-the- counter tests and that data that's generated, but perhaps stays in a lot of bathrooms because it's only the result for the individual. So we don't have access to that information. I want to thank you for reminding us of what was exposed there. Nilay, Nancy, Adrian, any reaction to Harvey's observations about the generation of what resulted from millions of tests and then thinking about how we need to address that separately? Well, address the data following up. Yeah, Adrian, go ahead.

Adrian Hernandez (02:29:35):

Yeah, I think it's pretty clear when you look back in the retroscope for the pandemic, that without diagnostic testing we would have no idea where we were or where we're going. And so if anything in terms of a lesson learned was one, it was critically important to have that very quickly. There were certainly some challenges there, but the thing that stood out from this is just what was described. The collaboration between different organizations, so that there was actually a whole view of the mosaic of what was happening in the pandemic. And so I think that all of us owe the group's gratitude for doing that. There is no otherwise real radar for this, so thanks.

Susan C. Winckler (02:30:22):

Yeah. Adrian, I'm going to pick up on that, on the radar piece. I think the way you phrased it, now we can think about the diagnostic testing and the data, is both our windshield and our rear view mirror and perhaps being able to see outside of the vehicle and figure out where we're going and where we've been. So Harvey, we'll come back to you in the conversation as well, but thanks for generating that. Or maybe in my metaphor, cleaning off the windshield, scraping off the windshield and the back of the car. Nancy, let's pull you up to this. You had the opportunity to work with some more non-traditional sources of real-world data that generated helpful evidence, particularly more on the patient-generated side. So tell us about that experience and how you might look at real-world data and evidence differently now, in 2022, than you did in early 2020.

Nancy Dreyer (02:31:19):

Thank you very much. Thanks to everybody for all the great work and for the useful discussion. I'm intrigued the way so many people have used the words, "Safe space," because from a researcher's perspective, it was a safe space to talk about work in progress and help you get better. And I think that the ability to talk about lessons and challenges we were each encountering, in a timely fashion, really helped influence the course of ongoing and future work. So what IQVIA brought to the table was two types of atypical data, employer-generated data. And the examples I'll bring you are from professional sports and data reported from people about their COVID experience in the community outside of the hospital. Let me start with that direct-to-patient registry. I'm using the vernacular of direct-to-patient because that terminology is well understood.

(02:32:17):

But here we studied people who were not patients. We focus this online registry on the community experience of COVID, using person-generated health data about COVID symptoms, vaccines and side effects. Talking directly to people, we were able to solve some of the challenges others of you faced so we could ask them their race, we could ask them their ethnicity. Some of the lessons we learned, including identifying a triad of symptoms that were highly predictive of testing positive for COVID, which was especially important early on in the pandemic when it was difficult to get tested. We also generated real- world evidence comparing three marketed vaccines, in terms of their effectiveness against symptomatic and asymptomatic breakthrough infections, as well as side effects. We also were able to start to generate some information about long COVID symptoms.

(02:33:17):

But sharing the preliminary results for the Evidence Accelerator attracted FDA attention, subsequent collaboration and even some funding. Now, we were also able to contribute insights from two beautiful ecosystems. In these occupational health systems, both the NFL and the NBA have active occupational health programs in place long before this pandemic. We've been working with them to help keep players healthy. These platforms then became the backbones for daily COVID testing and mitigation programs. Now take the NFL, they implemented daily COVID testing in all their 32 clubs, which includes about 12,000 players and staff. Early in the pandemic, we learned from these data the cumulative player interactions, as short as 15 minutes and as near as six feet of someone who had contracted COVID, could result in transmission of infection.

(02:34:21):

Now these data were also used to generate head-to-head comparison of various diagnostic tests used by the clubs, since there was no mandating or supplies of, "Thou shalt use this test or that." So we were able to compare two reverse transcriptase PCR tests, to an antigen point of care test, and a transcription mediated amplification platform. So these data were published, but the long peer review cycle that we all encounter, I think it reduced the opportunity for others to take action from the information. But because of the active dialogue in the Evidence Accelerator meetings, Christina Mack who led this work for IQVIA, was able to share our findings, which later led to follow-up discussions with CDC, FDA and product manufacturers, including very practical, actionable discussions on testing and purchasing. From the NBA, we learned more about disease transmission, specifically once players were no longer symptomatic after they'd been diagnosed with COVID.

(02:35:27):

Many still tested positive long after their symptoms resolved, but there was no evidence that these players, with persistent positive tests, actually transmitted infections to other players or referees. Now these were data from the NBA bubble, so really complete data on population that couldn't avoid being followed. The NBA also had really useful data on vaccine effectiveness in preventing incident symptomatic infections. Again, this was published in JAMA, but the Evidence Accelerator gave notification to important stakeholders even before the publication could go to press. So how's that for something a little out of the ordinary?

Susan C. Winckler (02:36:12):

Nancy, I'm reflecting. I will say that some of those presentations changed my behavior when I had a breakthrough infection about a year ago. So N of one, but we know it was an N of more than one from the folks who were listening and engaging in the accelerator. And as you noted, and I think about the power of Harvey mentioning the numbers of diagnostic tests and just the testing and the view that provided us. But then your observation, "That you could go and get the data more directly in those bubbles, as well in some of the patient-generated data," it helps close some of those loops, close some of those holes rather, which then, Nilay, I think is a great way to turn to you. We had the occupational health component, which was part of what Nancy shared. But I have to say, you, like me and many others, you're now in a different professional role than in early 2020. But talk to us about the engagement with real-world data on the employer side and differences in how you think about real-world data, versus in our pre pandemic life.

Nilay Shah (02:37:34):

Yeah, thanks Susan. It was interesting, at the beginning of the pandemic, I was at Mayo Clinic and we were doing a lot of work. And actually, in one of the prior presentations with Nancy Lim, I was representing the Yale Mayo Clinic CERSI and participated in that project. And then part way through, I started at Delta Airlines. One of the key things that we recognize is oftentimes, we needed data and information at much sooner rates than we could get through typical approaches waiting through other sources. And so set up relatively early on in the process ways to get data and build a data infrastructure and even the definitions of data.

(02:38:23):

So we started capturing symptom data through a symptom self-checker, as well as the testing data. So we had initially the partners with Delta Airlines where Quest, and even now it is, but got a lot of data through Quest, in terms of the diagnostics, but also ultimately through the rapid antigen test as well. Got the vaccination data and, oftentimes, we couldn't get this data through typical streams. We couldn't get it through claims. We couldn't get it through healthcare providers because they were happening either through at airports, where it was onsite testing or onsite vaccination that was set up, that was just going through different data streams.

(02:39:07):

So we had to set up each of these data streams and similarly therapeutics. So even some of the approaches to getting access to Paxlovid or Remdesivir for some of our employees was a very different approach. We were able to build the data streams relatively early on, so we were able to track. We also provided pay protection, even still do, so we were able to also track infections. So when does someone test positive, they submit test data or we get it directly through either rapid tests or through Quest, for example. And so we were able to track infection, hospitalization, mortality, the full stream for all our employees. So that allowed us to sort launch [inaudible 02:39:56] track the impact of all the different pieces during the pandemic.

Nilay Shah (02:40:03):

Pieces during the pandemic. But it was interesting, there were no standards, right? We were getting data from laboratory providers, from pharmacies, from non-traditional healthcare providers, and trying to put it all in one place so we could actually track and ensure the well-being and safety of the workforce

overall. So, that led to a little bit of challenge in decision making like, "How do we store this data, how do we manage this data in a way that makes sense?" But we were able to then leverage the data for a variety of things. For example, relatively early on, we had people in our population, get all the different vaccines that were available, all three, and we were able to see very early signals that with one of the vaccines, we are getting higher rates of reinfection and higher rates of hospitalization. So this was at that time when it was just a single dose J&J vaccine. So, we were able to get really early signals that there was something different going on with that vaccination. The other piece is early on, we didn't have a very good sense of how well these rapid antigen tests worked. I think as Nancy alluded to, we were able to take them and have a gold standard for those that underwent laboratory-based testing to see which ones are we seeing, what's the performance of each of those tests, especially in terms of sensitivity of those tests.

(02:41:34):

So, we were able to leverage this and one of the things coming from that healthcare background where you really think of real-world evidence very much in the context of electronic health record data and claims data, and you have limited sources of data that you think of, and you realize how much happens outside of those traditional data streams. So it gave me, at least from my perspective, a real different lens on the real- world data as well as real-world evidence where you may have missing data if you just look at the electronic health record data and claims data. So it really will be an important piece going forward to start thinking about what other data streams that we need to think about very similar to all the things that Nancy alluded to as well.

Susan C. Winckler (02:42:22):

So, Nilay, you helped me as I was thinking through the inevitable metaphor that emerges that we started with Harvey saying we've got the windshield and the rearview mirror. And then Nancy, I think I interpreted yours being able to go to the patient level and data performance is maybe when we put on our glasses to be able to see better. Nilay I think you pointed out, we can also look out the side and look to things other than claims and EHR to get information, but then that also creates the challenges that you had to navigate of how do you store it using it. Then we were all presented with how do you link in data sources from vaccinations administered in stadium and tracking that. And if not, then also what it means if you don't have the evidence of vaccination, but they may have had it somewhere else?

(02:43:21):

So thank you for working through some of those challenges to help us understand how to look at other data sources. That takes me that I'm going to turn Adrian to you because you're probably laughing at my metaphor because you're like, "Of course, I've been thinking about all these different sources of real-world data." So you have a different perch where you see all those sources and the evidence that it generates. So let's add your voice to this. What do you think about as what's different and how are we better positioned to perhaps change gathering and evaluation of real-world data as well as then application of it?

Adrian Hernandez (02:44:08):

Yeah, so I think we just heard a number of different examples that using rural data gives us a better understanding of what's so-called happening to people across different communities. It's not just

around electronic health data that's actually tying all the things together. I think one of the things we learned through the experience is that the questions we're trying to address really do matter. So some of the examples that we just heard from were they're really key epidemiological questions, where's the illness going? Where's the pandemic going? What are the things that we need to be thinking about in the coming months? What are those emerging signals say breakthrough infections or hot spots or perhaps effectiveness issues in terms of different treatments because of how rapid we're seeing variants emerge? However, there was one thing that I'm just going to remind people, especially in the first six months, first year of the pandemic, is that there's so many different questions that were coming up.

(02:45:15):

It was like popcorn, we didn't have all the right answers or the tools to do it. So there are a couple of key things that seems like one is prioritization of the questions. So as a community, how that was prioritized and actually coordinated so that different parties could actually help address the same question perhaps with different data and even perhaps different methods other? The second thing is that there's some questions that are not going to necessarily be answerable reliably with observational methods. So that's why we do need to have randomized trials that can use [inaudible 02:45:52] data, not do separate and be separate. So an example of that as we're seeing this, and I can't remember who to actually give credit for this, but we tend a viewpoint on this observational cacophony that we're just seeing this popcorn of all sorts of observational studies to do this, do this, do this.

(02:46:09):

And actually, it turns out one study may say that treatment is good, one study may say a treatment is harmful. It turns out the truth was actually somewhere in the middle that it was neither so good or so bad. Then there are some cases where we were surprised until the randomized trials were done leveraging rural data. So all of us, I think have enjoyed the benefits, for example of the UK recovery study and so how we can do that more is going to be really important. Then also how to be honest with ourselves that observational methods may not necessarily be a fit for that purpose, but certainly some of the examples that we just heard from are understanding effectiveness of vaccines. That has been a tremendous learning as we've gone along.

Susan C. Winckler (02:46:58):

Really helpful, Adrian and I was thinking that the observational cacophony that you referred to, if we go back to being able to see out of our vehicle, it may be that then we're also getting notifications of things that we're supposed to pay attention to, but they're nonsensical or they're not aligned with that. Harvey, you unmuted, Do you want to jump in?

Harvey Kaufman (02:47:21):

Yeah, it's sort of driving down Fifth Avenue in Manhattan. There's so many just visual distractions you don't know what to look at. And what happened during this pandemic is one, there was a lot of pre-print publications that were put out, enormous number of publications and it was really impossible to sort out what was real and what wasn't real. There was a study looking at ABO Rh that got a lot of media attention. We did the same study but then overlaid race, ethnicity data and showed that there really wasn't a relationship. But the first study was in John [inaudible 02:48:00] got a lot of attention, but it was hard to figure out what is the truth. And it did change, particularly as we had new variants.

Susan C. Winckler (02:48:11):

Really helpful and I appreciate that you are continuing the metaphor even better with going down Fifth Avenue and all the things that are going on around you. So let's then think each of you had been involved with the COVID-19 Evidence Accelerator as well as are continuing to work in real-world evidence. So I put a question to all of you, and I'll turn to whoever unmutes first, but share with us where do you see the most promise for real-world data and real-world evidence as we're looking forward. Then was there anything about the COVID-19 Evidence Accelerator that can help us pursue that promise? So think about that. Nancy, you're first to unmute, which I was going to say that you and Harvey should get the merit badge for most active chat participants during Evidence Accelerator, but now you unmuted faster so go.

Nancy Dreyer (02:49:13):

I don't know what to do with that award. But first of all, Adrian, always, I like hearing from everybody, but I have to remind you that not all clinical trials agree with each other either. So the fact that we had real-world evidence that showed different things and as we learned we got better, I don't think it doesn't argue for one or the other, but it doesn't mean the real-world evidence is wrong just because it didn't agree, assuming all trials would. But putting that aside, Susan, I think because we can continue that discussion as I know we will, but I think one of the big, big lessons we should all be taking home from this, and Susan you've brought this to light for everybody, is we need to rethink this concept of representativeness and what it means. Because you look at all these guidelines and they say it's important to have complete and representative data and we all nod.

(02:50:05):

But I think what we've heard today, the big lesson here is that I don't think every study needs to, or we need to rethink our traditional definition of representativeness. Very specialized populations can contribute important actionable information. Now, nobody would say that the NFL or the NBA is representative of US residents. None of these people on the phone either but we learned valuable generalizable information from them. Susan, you changed your behavior, and just like people who participate in the online surveys are not representative, doesn't mean they can't be informative with the right study designs and the analytic approaches.

Susan C. Winckler (02:50:49):

So we should take the opportunity to look where we have the opportunity to and then put it into context. Yeah.

Nancy Dreyer (02:50:55):

Sorry, on the metaphor. Yes.

Susan C. Winckler (02:50:56):

Yeah, Harvey, you were second on the unmute.

Harvey Kaufman (02:50:59):

Okay. So to continue the metaphor, we have historically focused on the rearview mirror. So if you look at data that's put out by the CDC, it is typically years after the fact. I think the most recent data on pediatric led is 2018. It is hard to go ahead and manage healthcare, particularly in a pandemic, but with looking at data that is old. And what we learned is real-time data counts and real-world data is the way to get there. Then one little gripe, US Preventive Services Task Force still refuses to acknowledge real-world data and that's I think a shortcoming of the US Preventative Services Task Force. We know that real-world data complements other data

Susan C. Winckler (02:51:53):

Really helpful and nice point to be thinking about where it might otherwise be applicable. Adrian. Adrian, Nilay, Nilay, I'll turn to you last. Adrian.

Adrian Hernandez (02:52:03):

Yeah, no, well I certainly can't disagree with Nancy that there's actually purposes for using real-world data, both observational and prospective randomized trials. So I think a couple things that we saw here clearly is that different stages of the pandemic, it's really important to emphasize that take advantage of the methods that are available that give insights at the time and the context that's needed. So very early in the pandemic, understanding different issues about risk factors et cetera is really important where the pandemic was going. Later in terms of actually inserting randomization with real-world data to generate the evidence of how to treat patients is important.

(02:52:49):

Then later as treatments were being used to understand either the loss of effectiveness or other issues that came about that were unobserved during the randomized clinical trials is also critical. So the myocarditis is a good example of that. So again, we wouldn't necessarily pick that up and say the clinical trial because the size, but it's very clear that was very helpful to understand and also the relative difference of those cases in the real world setting, unvaccinated versus vaccinated as well, to put it all in perspective. So I think we should have all of it.

Susan C. Winckler (02:53:28):

We should be thinking through it, how to use all of the different ways that we can look and gather information. Nilay, what do you want to chime in here?

Nilay Shah (02:53:36):

Yeah, no, I agree with everything Adrian just said, but I think the one piece that in retrospect what we thought about, what could we have done differently to get better evidence to help our people along the way? One of the things I think that's sort of a middle ground between real-world evidence and more robust evidence is could we have done natural experiments. So our population is spread out all over the country and could we have provided for example, the rapid antigen test in one part that's test A, test B in a different part, testing and be able to evaluate them more real-time with a little bit less of a selection bias, maybe going into some of that. So again, not perfect, but we could have leveraged some of those type of designs. And not for every question obviously, but where you're trying to compare certain

alternatives, that's another approach which brings together, you can still leverage the real-world evidence, but maybe you have a little bit more of an experimental design built into it.

Susan C. Winckler (02:54:41):

Really like that and you're getting head nods from Adrian and Nancy in the real-world evidence and the clinical trial piece thereof that we could have another opportunity and an opportunity beyond the bubble of the NFL, NBA to that more real-world experience in the airline situation. Well, that brings us to the close of this panel. So I want to give you each an opportunity, if there's one thing that you could have perhaps put in front of the Evidence Accelerator or you heard on the evidence accelerator that you wish everyone else had heard, what might that have been? So let's go, Adrian.

Adrian Hernandez (02:55:34):

The one word that just comes up over and over is collaboration. People are all in and so if we were actually to turn this forward to other major health problems, we could learn faster and better I think. So just some process of how all the organizations came together.

Susan C. Winckler (02:55:55):

Great collaboration will go in our word cloud. Nancy.

Adrian Hernandez (02:55:59):

And just sharing and also importantly sharing mistakes. And so sharing lessons learned. So that was the thing that when I meant collaboration, it's like actually pitfalls sharing this.

Susan C. Winckler (02:56:12):

It wasn't just we're awesome and here's the great work that we did. It was a bit of tough to figure out. Nancy.

Nancy Dreyer (02:56:21):

Well, I would extend that comment, Susan and Adrian, not just to mistakes we made, but here's what I'm struggling with and we've heard all the struggles that were totally reasonable for the time. So I think that ability to get beyond your institution so that collaboration is see the way somebody else thought about it, turned on light bulbs. But I think also one of the lessons that you brought to life or to light here was the value about keep broadening the mix of the real-world data. Because we have a lot of sources we've started to really refine and get good, but let's keep looking. There are so many, the advent of wearables and there are just so many different tools we could start to call on now. Let's keep thinking big.

Susan C. Winckler (02:57:08):

Excellent. Harvey.

Harvey Kaufman (02:57:10):

Without it alarming the privacy folks, the ability to have collected identifiable data across all systems would've been beautiful and so where everyone got treated or vaccinated, the ability to have the government, CDC, or otherwise collect that data and then have the appropriate folks analyze it would've been a beautiful thing.

Susan C. Winckler (02:57:39):

Right. To have a patient-centric repository versus as we saw in our diagnostic test information, I'm pretty sure mine's in about six different places and that's true for so many people. Nilay.

Nilay Shah (02:57:55):

Yeah, the only additional piece I would add is I think just the ability to bring the many different streams of data in a single environment and be able to talk to each other. I think that was really unique. I don't think that has always happened in any other environment. Then be able to see what is being generated through each of those different streams I think was invaluable all through the pandemic.

Susan C. Winckler (02:58:22):

Yeah. To be able to be like, okay, so here's what showed up in EHR, and here's what we see in claims, and then here's what we see in that NBA, NFL bubble and from the employer on the airline side and then from the labs themselves, all different, different opportunities there. Well with that, thank you so very much for joining us to think about, take that step up and think about what did we learn in swimming in that sea of real-world data. Now we have our new metaphor about having a lot more visibility and Harvey, we're going to start looking forward instead of trying to drive through the rearview mirror. So thank you all so much for your contributions to the evidence accelerator and for joining us today. And with that, I'm going take us to our closing conversation. I am going to ask Dr. Ellen Sigal to step to the microphone and turn on the video. I see you, Dr. Sigal.

Closing Thoughts

Susan C. Winckler, RPh, Esq., *CEO, FDA Foundation*

Ellen V. Sigal, PhD, *Chairperson and Founder, Friends of Cancer Research, and Chair of Board of Directors, FDA Foundation*

Ellen V. Sigal (02:59:23):

Oh wow. What a session. Yeah. Oh my God, thank you. You must be exhausted.

Susan C. Winckler (02:59:32):

Well, I have to say, Ellen, you opened and sat through so many of our lab meetings and our parallel analysis meetings and they were so often just like that last panel where we could hear different things and learn and just a fascinating piece, but that's my reflection. Tell me what you were often the opening word for every single of these lab meetings-

Ellen V. Sigal (03:00:04):

I was opening that was easy. You did all the work and the foundation. Well, first of all, I want to start with great appreciation. Thanks to you Susan. You came in, you just came in and this just happened. It was just extraordinary. I don't even know how long you were with us when this happened. Not long. Right?

Susan C. Winckler (03:00:24):

You even started before I got there, so I jumped in. I think meeting number three or something.

Ellen V. Sigal (03:00:29):

The fact that you didn't jump out is pretty extraordinary but really I do mean it. Sincere thanks to you and the extraordinary team at Reagan-Udall, people worked around the clock. This was a huge urgent need and people came to the plate and they did everything they could and we have to understand how we do understand. I mean, I think in earlier we were talking about Fifth Avenue, I'd say Times Square Broadway. It was crazy. It was crazy times. So I come with great appreciation and frankly just in awe in what was accomplished in that period of time.

Susan C. Winckler (03:01:15):

Absolutely. I think it's as Adrian had just reminded us about the collaboration and the partnership and people talking with each other, the partnership that we had with Friends of Cancer Research, which you brokered was so very helpful. So how do you think about partnerships like that kind of moving forward? Is there an opportunity to say something that doesn't happen in Washington very often? Maybe you get together for a coalition letterhead, but to actually do an enduring project and work together. Just say a little bit about that.

Ellen V. Sigal (03:01:54):

It's pretty extraordinary. Friends of Cancer Research and Jeff Allen in the group has a lot of experience in bringing people together, but frankly in a very orderly, methodical way where we can do it over a period of months and we have time to go back and forth with drafts. This was just a tidal wave. You had to jump in and get it done and I'm very grateful to Jeff and the team of Friends, but I'm also very grateful to you and the team at Reagan-Udall and FDA were willing to do that. So the urgency because of the pandemic was huge. The complexity, as you know is to do it, but to try to get it right and that was really, really, really, really hard because yes, we needed answers and we needed urgent answers. And the community did come together, not just friends, everybody on this.

(03:02:51):

Everybody in the community came together, people at FDA came together, people in the private sector, data aggregators who don't normally work together did it. So from that point of view, we have to be extraordinarily proud and they came together because we really had a pandemic and it was urgency and it was different. Nobody needed their name on top of the letterhead. It was just a matter of just we need to solve some problems. We have some data, you have some data. How do we put it together? It could be very messy. And I think we tried very hard, Susan, you know that the team to really get it right. So the challenge was how to get some data with some urgency, but try to make it as accurate as it could

be. And that was really very, very, very complicated. But we accomplished a huge amount and we can be very proud.

(03:03:46):

But you're right when you go to the future now, how do we now not go back into our silos? We saw that at FDA. At NIH, we saw that with these extraordinary active trials that everyone came together, they did it, they did it quickly, processes went away. And there was a goal of getting better medications to vaccines, to patients, medications, and diagnostics. So the challenge I think that we face is not, what we accomplished with all the enthusiasm and organic coming together is how do we keep it going and how do we galvanize some of that? Because we do know that our silos don't work.

Susan C. Winckler (03:04:29):

So well stated, Ellen, that the need for collaboration and to think about, or we were just using a metaphor of not only using real-world data in the rearview mirror but using it to look forward and then gathering different sources of real-world data. So looking to the side and navigating through all of that information, we have an opportunity now to make better use of all of that available information and that's a piece that we need to remain committed to doing. So, Ellen, I think I'm going to let that be our last word, that we have to maintain the commitment to continuing to the rigorous transparent evaluation of real-world data to help us better see things in real-world evidence.

Ellen V. Sigal (03:05:16):

Get out of our silos and work together and work for the patient and work for the common good. So thank you and again, that's why Reagan-Udall was started to do exactly this thing.

Susan C. Winckler (03:05:30):

And we're pleased to have had the opportunity. With that, I'm going to say thank you to everyone for our speakers, our panelists, to each of you who attended the meeting today. So those who have participated in Evidence Accelerator meetings since April of 2020. We will be posting the recording of this event on the Evidence Accelerator website later today, and we will add the event transcript within a few days. With that, thank you so much. Take care and we'll hope that we see you soon.