Webinar 2: Research Session 2: Focus on Real-World Data

PATTI JEWELL, *Pfizer*: My name is Patti Jewell, and I am Senior Director of Patient Advocacy for Pfizer. On behalf of Pfizer colleagues around the world, thank you for taking the time to be with us. This webinar series was inspired by a meeting with breast cancer advocates from 24 countries who developed a list of 81 ways to improve breast cancer care.

If you can go to the next slide, please. A key topic of interest was to learn more about research and how patient advocates can support patient participation in clinical trials and other types of research. This webinar is the second in a series that Pfizer's hosting to support breast cancer advocates, to learn more from subject matter experts and each other. For our session today, we'll focus on real-world data, what it is, how is it used? And how is it relevant to patients?

Next slide please. So we're recording this webinar today to help us share the content and ideas with those in the advocacy community who are not able to listen live today. Please remain on mute to avoid background noise, and we encourage you to submit your questions using the Q&A function. You can find this on the lower-right side to of your screen. You'll see three little dots and if you click on that, you'll see the Q&A function pop up and you can type your question in that. We've reserved the last 15 minutes of this webinar for your questions.

Next slide, please. The first webinar in our series provided an overview of research and medicine development. Advocacy leaders from the Cancer Support Community and breastcancertrials.org shared how they educate patients about clinical trials and the resources that they develop to help patients find

a trial that may be right for them. You can visit their websites to learn more about these resources or be in touch directly with the leaders, just email me and I can connect you over email to them. The recording and transcript for that webinar will be posted on breastcancervision.com in the near future. And we will notify you when that happens.

Next slide, please. Additionally, it's really important to Pfizer and the advocacy leaders with whom we work that these webinars connect back to that list of 81 actionable solutions that we develop together. On this slide, you can see a few examples of resources from around the world that exist to support educating patients about research, such as an advocacy training course from Europa Donna clinical trials registries in the European Union and the US and the use of digital platforms to reach patients. You can find these and the full list of ideas and solutions in eight languages on BreastCancerVision.com.

Next slide, please. None of this work would be possible without our planning committee of six advocacy leaders who work together in deciding what specific topics to focus on for these webinars. Many thanks to Bertha Aguilar of Mexico, Conchi Biurrun of Spain, Renate Haidinger of Germany, Stacy Lewis of the United States, Shirley Mertz of the United States, and Ranjit Kaur of Malaysia, for taking their time to share their insights and ideas that are informing this and future sessions.

I'd now like to turn this over to Shirley Mertz to lead today's session. Shirley has been living with metastatic breast cancer since 2003. She was an educator and high school principal and is currently the president of the Metastatic Breast Cancer Network in the US and is a member of the board of directors of the ABC Global Alliance. Shirley, over to you.

SHIRLEY MERTZ, *Metastatic Breast Cancer Network:*
Thank you, Patti and welcome to all of you who are here to joining us. I hope this will be very educational and also actionable. As you see by this chart, we're going to begin with a presentation on real-world data and evidence. What is it and why is it being used? And after for that, we will go to a patient perspective, offered by a very active advocate on the world scene. And then as Patti pointed out to you, we will have 15 minutes of Q&A. And I do along with Patti's reminder, if you will look at the far-right lower side of your computer, you should see three dots. And if you click on those, there will be a space in the Q&A for you to write a question. And we will monitor those and pose them to the appropriate speaker.

And then we'll have two minutes more where Patti will close the session and offer you any further contacts for you to pursue. So again, welcome everyone. I would like to begin by introducing our first speaker. His name is Dr. Jeremy Rassen. He is pharmacoepidemiologist with 25 years of academic and industry experience. He is Co-Founder and President of Aetion, a healthcare technology company that delivers real world evidence for life-sciences companies, payers, and regulatory agencies. Prior to founding Aetion, Dr. Rassen was assistant professor of medicine at Harvard Medical School, where he focused on methods to improve the quality and validity of real-world data studies. Dr. Rassen is also a fellow of the International Society for Pharmacoepidemiology. Welcome Dr. Rassen and I will turn it over to you.

JEREMY RASSON, MS, ScD, *Aetion:*

Thank you so much for allowing me to join this morning and good morning, good afternoon, and good evening to everyone on the call today. I will be speaking if we go to the next slide about precisely the topic you mentioned, which is real-world data and real-world evidence, what it is and what we can learn from it. I wanted to give a little bit of perspective before I dive into any of the details. This was an article from about 10, 12 years ago, written by Andy Grove, who is the former CEO of Intel about rethinking clinical trials.

And he had this vision, which seemed a little bit impossible at that moment, but very possible today about how we could use data, data that comes from the routine operation of the healthcare system. And there can be insurance data or electronic medical record data, other kinds of data, certainly including registries as well, to understand the safety and effectiveness of medications beyond what we learn in a clinical trial. And as I said, when I read this 10, 12 years ago, I thought that's a nice vision, but I don't see it being possible today. So much has changed worldwide in the last 10 years that I think this vision has become a true reality and I'll explain that over the next 15, 20 minutes or so.

On the next slide. I want to just sync on two definitions, and you'll hear two terms here or two abbreviations very frequently. The first is RWD, real-world data, the second is RWE, real-world evidence. And so I'm going to use the FDA's definitions of these two terms. So real-world data is data relating to patient health status and/or delivery of healthcare that's routinely collected in the operation of the healthcare system. Things like electronic healthcare records, insurance claims, registries as they're collected, patient reported outcomes and so forth. Real-world evidence, on the other hand is clinical evidence about the usage and potential benefits or risks of a medical product that's derived from the analysis of those real-world data. And so sometimes you'll hear the terms used a bit interchangeably, but I think of the RWD as the data itself and the RWE as the evidence that we can understand from having analyzed those data.

So I just wanted to put that out there as we began here. On the next slide, why are we talking about real-world evidence? And what's so compelling about it? And Renate will certainly give a further perspective on this. But I'll just say broadly speaking, that real-world evidence provides us the opportunity to ask more questions, understand broader populations and generate more evidence than we could feasibly do in the context of clinical trials. I think from the topic last time and from experience, I think many will understand what we can and, but also possibly what we cannot understand in the context of clinical trials, given the limitations of running a trial, that the challenges of running trials. We have many more questions that we need answered about our medical products than we can feasibly answer with clinical trials.

And so real-world evidence very broadly provides us the opportunity to ask those questions and get those answers beyond the clinical trial context. We have to be thoughtful about what we ask and to make sure that we ask questions that the data can really answer. We have to be thoughtful about how we answer that question, how we analyze the data to make sure that we're getting results that are substantive, but there is an incredible opportunity with real-world data and real-world evidence to ask many more questions than we'd be able to do otherwise. And as I said, we'll hear more about this in the next talk.

On the next slide, I want to note that real-world evidence compliments the evidence that we get from randomized trials. And I think many will know these randomized trials help us understand the efficacy of a drug in a controlled setting. And that controlled setting is the parameters of the clinical trial, how the drug is utilized, how the outcomes are monitored. And so this is a treatment, as I said, in a highly monitored controlled environment that's part of the trial setup. The intervention, which is to say that the treatment that a patient receives as part of that trial is strictly enforced and standardized.

That's very different from the real world. And that's very different from what we can understand from real-world evidence. So real-world evidence looks at the effectiveness of a drug in an everyday clinical setting. And the treatment is part of routine clinical practice at the discretion of the treating physician and in consultation with patients but isn't in that formalized environment of the randomized trial.

And so, often, you'll hear of randomized trials as being the gold standard of data. I like to think of the randomized trials as being a gold standard. So it gold standard for understanding the efficacy of drug in a controlled environment, but maybe not the gold standard in that there's much more that we want to understand about a medication in particular, how that medication works in real everyday settings, and thus we can understand that through real-world evidence. And so we can think of having multiple gold standards, if you will, about how medications work.

If we go to the next slide. Why are we talking about this increased interest in real-world evidence? What has changed since Andy Grove, for example, published that article 10 or 12 years ago? There's been large changes worldwide in technology and the analytics available. There's been a growing variety of data sources and also on the receiving and understanding of the data, certainly increased the appetite for real-world data and real-world evidence from regulatory agencies, health technology assessment agencies, and payers worldwide.

People are really looking to understand how medications perform in the real world and that's of course not to mention patients, clinicians, and others who are providing and receiving care really very much interested in this gold standard of information about the performance effectiveness and safety of medications. So, on the next slide.

Where do we get the real-world data? And so that's a fundamental question we can certainly talk more about this. A couple of places in the United States, there is a large amount of commercial insurance claims and billing activities that can serve as the source of the data. Electronic health records, lab data, national disease registries, product registries, patient-generated data, and other, has become sources for real-world data. What's not here, of course, is data for randomized trials, that's the clinical trial data. Almost everything else can be considered real-world data for the purposes of this discussion.

So on the next slide. I wanted to note that this is really something that's happening globally. And I'm giving the example here of the global regulatory agencies, because as I said, we're looking to understand the performance of medications. Clearly, the regulatory agencies are at the forefront of needing to understand that as part of their regulatory activity. So, I

wanted to show that the Food and Drug Administration, the FDA here in the United States, the European Medicines Agency in the European Union, the NMPA in China, Health Canada, PMD in Japan, MHRA in the UK, all have very active real-world data and real-world evidence programs where they're explaining and helping the community to understand what they expect in evidence that's generated from the real world, so that they can analyze that evidence and understand this real-world performance.

And so, this is a very active area, the Food and Drug Administration here in the United States, for example, released a 40-page guide draft guidance about a month or two ago, there is an active commentary being submitted to the agency so that they can understand points of you from around the field and incorporate those points of view into their final guidance. This is guidance on the use and creation of real-world data. There'll be further guidance that help understand further aspects of the field, but that's one example of many that are going on in parallel around the world.

So on the next slide. Now, I want to be straightforward here and say that, this is not without some discussion, let's say. And so you can see this article here from the new England Journal of Medicine, February, 2020, "The Magic of Randomization." And I will be the first to say that that randomization is magic in many ways versus the myth they say of real-world evidence.

Matt Herper in STAT attempt to replicate clinical trials where the real-world data generates real-world criticism too. So, I wouldn't say it's the myth of real-world data, I don't agree with that part. But I think some demystification, if you will, can be very helpful in understanding what real-world data, real-world evidence can do. And very importantly also, what it can't do. So, I wanted to give a little bit of perspective on that over the next few minutes, if we go to the next slide.

I want to take a, quote, unquote, simple question. Let's think about how to use real-world data, real-world evidence to answer the question of, do statin medications lower the risk of heart attack? And this is, as I say, on the surface, a very simple question in a widely used medication a very common outcome. And if we looked at the real-world data, if you go to the next slide, if you look at it without thinking further about it, you would say that statins double the risk of MI. And that's certainly not true, statins lower the risk of MI substantially. But in the real world, patients are taking statins because they're at risk of MI.

So patients who are taking statins are at a very much higher risk of MI, myocardial infarction, heart attack, than patients who are not. And so, if you look at that data naively in the real world, you would come to a conclusion that is absolutely incorrect. So how do you come to a conclusion that's correct using real-world data where patients are not randomized to statin or no statin. But rather are treated in way that their clinicians in consultation with them feel most appropriate.

So on the next slide. This is the field of causality, and it's a big field. There's a lot of academic and other thinking about this, both very technical, philosophical, all kinds of angles. I particularly like this book here, you have the image of, it's the, "The Book of Why."

It's by Judea Pearl written with Dana McKenzie. Judea Pearl has been writing for many, many years about causality, but often in ways that are highly academic. This is a book that he wrote in collaboration with Dana McKenzie, that I find very, very readable. And I wanted to use a figure on the next slide from the introduction of this book, to think about what it means to establish causality. And so, you can see the figure on the right side here. And he and McKenzie present what they call a causal ladder.

And the first rung of the causal ladder is what they call associations. So statins in the real world are associated with a higher risk of MI. So do statins raise the risk of MI? Maybe, maybe not. But when you hear that causation is not association or correlation, that's this first rung of the ladder. And Association give us clues about what drugs might do. But interventions, the second rung allow us to demonstrate that a particular drug caused a particular effect. If I take a statin, my risk of MI will go down.

And interventions are very much the domain, if you will, of randomized trials. So the there's an intervention, a patient enrolls in a trial, a virtual coin is flipped and a patient is directed toward the take the statin group versus the placebo group, for example. And by analyzing those data some amount of time later, you can see that statins do indeed lower in the risk of MI. There's a third rung, which is counterfactuals, which help us think about why a drug does what it does, but we're thinking mainly around the second area of interventions, because that's a primary interest, does a drug lower the risk of a particular negative outcome? And so, as I said, randomized trials are the primary source of that information to date.

But on the next slide, you can see that real-world evidence can give us that answer as well. If you do it in a way that fundamentally understands where the data comes from fundamentally understands how the data represent the patients that a patient in a real-world data set will have gotten, in our example here, a statin because they were at higher risk of MI.

And on the next slide is a quote that I find really interesting. And sorry, it's a little bit technical and a little bit long, but I want to go through it. Pearl says, "Successful predictions of the effects of interventions can sometimes be made even without an experiment." So, even without say a randomized trial. A sufficiently strong and accurate causal model can allow us to use rung one observation alert or real-world data to answer rung two, interventional or traditionally randomized trial queries.

And without that causal model, we could not go from rung one to rung two. And I've spent the better part of my career thinking about how we create those sufficiently strong and accurate causal models so that we can do precisely that, we can understand causally, what affects drugs have through the use of observed or real-world data. And so, I like that he draws the connection here between how we can traditionally use real-world data, real-world evidence, and that's in that area of associations, but how we can analyze those data in a very thoughtful, a very careful way and understand the causal effect, the intervention effect, if you will, of those medications.

So on the next slide. We like RCTs. I love RCTs. I mean, don't get me wrong. I love randomized trials, because they're an easy way to create that strong causal model that Pearl talks about. But if we apply a principled process and again, that's what I've been thinking about with colleagues and a large community of researchers, real-world evidence can be equally effective in many cases. And as I said, it's on us as researchers to understand where real-world evidence can be equally affected and where it might be less effective. And to be very honest and very open, very straightforward about that and make good choices about where we look to real-world evidence to provide us information versus other methods, for example, clinical trials.

On the next slide. This is my takeaway here, my summary. We need good, randomized trials combined with good high quality real-world evidence. And what is good high-quality, real-world evidence? There's a lot of discussion about that these FDA and other agency guidance that are coming about help us understand that more formally in terms of what the regulatory agencies are expecting. But fundamentally neither real randomized trials nor real evidence alone, provide the full picture.

Again, there isn't one gold standard, there's multiple views of the performance of a medication that we need as a community to understand. And we need as a result, both of these methods, randomized trials and real-world evidence complimenting one another to truly understand how a medication works in the clinic, but also in the real world. So I'll leave it at that and say, thank you. And looking forward to any questions you might have at the end of our session. So, thank you very much.

SHIRLEY MERTZ, *Metastatic Breast Cancer Network:*
Thank you, Dr. Rassen. That was fascinating. And I know we have some questions coming up for you. But now I'd like to turn to our next speaker, Renate Haidinger. She is a medical journalist and the Founder and President of the German Breast Cancer Association. Renate has been a breast cancer survivor since 2000. And currently, she specialized on educating on breast cancer through doing interviews with experts at all relevant conferences. Renate serves as the chair of an international patient advocate subcommittee for the International Abreast Registry, a member of the advisory board of the Success Clinical Trials, and also part of the independent data monitoring, excuse me, committee of a large German study group. She is also director of the General Assembly of the ABC global Alliance. Welcome, Renate. We're anxious to hear what you have to say.

RENATE HAIDINGER, *German Breast Cancer Association:*
Thank you very much, Shirley, for the nice introduction. Yes, we heard about a lot about real world data and real-world evidence. But what does it mean for patients, their perspective, and also the decision making? So, what is it? It's all about the patient and the patient is, or should be, in the center of real-world evidence. In randomized clinical trials that we already heard, we have some limitations because of inclusion and exclusion criteria and so on. And we have a predefined group of patients that do not reflect all patients that are treated with medications in the real world. Next slide please.

So what does this mean? In the real world, treatments are also given to elderly patients, which might be completely different, and I tell you later why, then we have a variety of

race, gender ethnicities. And very often some are overrepresented, and others are underrepresented in clinical trials. Then we have patients with other comorbidities. So, what does that mean for a medication? And also we have patients because of that, who take multiple medications. And as a consequence of this, treatments may work completely different or somehow different than what that was observed in the clinical trials. And on top, additionally, different side effects may occur, or new drug interactions may be identified in the real world. Next slide, please.

So the patient is the one who has to live with the treatment, and they therefore know best and what it means for them on an individual level. When physicians suggest a treatment, patients want to know quite a lot. Like, how does it work? Did this medication work for other patients? What side effects did they encounter? Might be completely different for each individual, but at least to know what might come up. How will it impact my quality of life? Will I be able to do my daily tasks? Can I take care of my children? Can I still go to work? So, it might have a big impact on the quality of life. How long did the treatment work? There are a lot of patients that want to know the best and the worst scenario. Usually, we only hear the best scenario there is. And also what is more and more important as even metastatic patients live longer now, with the very individualized treatments, what are the long term data of side effects, for example? So, these are all things patients want to know before they start a new treatment. Next slide, please.

So what is the role of patient groups and their advocates in this? We have an important role. They can support and give input to a lot of things, like observational studies, standardized and fitted questionnaires. And I will show you an example of that. We can educate, we can define information in the lay language so that everybody can understand it, and it's required for decision making and together with the patients. They can be the missing link between randomized clinical trials, real world data, and real-world evidence. Next slide, please.

So, we, for example, did a survey, an online survey on our website and on Facebook. Because by counseling between seven and 8000 patients a year in Germany, we found out or got the feeling, that the side effects and the long-term side effects, especially, might be very different from what we learned from clinical trials. So, we asked in early breast cancer patients, a long questionnaire about the side effects they still encounter after having finished their treatments. And what came out of this and we published it in Breast Care, that chemotherapy associated with increased rates of long term symptoms. And long-term peripheral neuropathy is much underestimated, and it doesn't always go away within one year. Next slide, please.

So as take-home message, the better treatments can be personalized the more we need data from patients outside of clinical trials. So, we need real world data and real-world evidence. And does the medication work as well in the excluded part of patients, portion of patients like older patients, and different races, genders, ethnicities? What about patients with comorbidities and patients who take multiple medications? What is it about the safety for them, the side effects, interaction of drugs, food, herbs, et cetera, and above all, for the quality of life? Give patients as much information as possible about the results outside of randomized clinical trials means a lot for the patients to understand what the treatment

might do, maybe what kind of harm, smaller and bigger it might do, what side effects and what they need to know. And the more that precise treatments are investigated in randomized clinical trials, the more important it is that we explore the experiences of all types of patients in the real world. Next slide, please.

So what we started in 2005, because there was such a big need of information still, and it still is that we do, or I do, video interviews with German experts at all big conferences, all over the world concerning breast cancer, and they explain the new data that came up during the conference by now lay language. In the beginning, it was quite difficult because they used the medical terms, which weren't understandable for everybody. And then I had to ask them to explain them. By now, they even explain them themselves if they used a medical term. And these video interviews are so important for many patients and even some physicians that aren't so used to looking at presentations. And by now, because we had the situation with COVID-19 and all the different WebEx and Teams, and I don't know, Zoom, it's so much easier now to do video interviews, even online. So, I can really suggest that you might try out to do a video interview on a topic which is of very interest for all of you or your patients, and then explain exactly what it means for the patient, with a certain drug or with the daily life and everything they might encounter. Thank you very much.

SHIRLEY MERTZ, *Metastatic Breast Cancer Network:*
Thank you. Renate that was fascinating. And I'll have some questions for you in just a little bit.

RENATE HAIDINGER, *German Breast Cancer Association:*
Okay.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Renate explained one way in which her organization gathered data directly from patients through a survey. And I would like as a patient advocate to also share with you the example of a registry. As Patti mentioned, when she introduced us all, I am part of the Metastatic Breast Cancer Alliance in the States. And we established in the Alliance, a registry, a free mobile and web-based tool for metastatic breast cancer community. It's called MBC Connect. And it can be found at mbcconnect.org. And I'll just briefly tell you what it's about. It's available in English and Spanish. And the app allows patients to store their information about what type of disease they have, I'm referring to like subtypes, what treatments they've had, and what has resulted from those treatments, whether they worked for them for several months or years, whether they had to move on to another treatment. But this is a wonderful database.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
And the reason why we created it is that we wanted patients, first of all, to be able to go in and look at other patients anonymously, no one's names are given, but I could look up all other patients, say who have metastatic hormone-positive breast cancer and see what drugs they've been using and how successful that has been for them, and what maybe comorbidities they have that might be like me. And we also wanted this database to be available to researchers or clinicians who might want to do studies about particular groups

of people and use the database as a source of information. And I believe we have now nearly 600 people in the registry. So, if you are interested in looking at that, go to mbcconnect.org, and you can find out more information. And we also have it hooked up with a clinical trial base that can forward appropriate clinical trials.

So I'll stop there. And what I'd like to do is go to some questions. And Dr. Rassen, I have a question for you. I'm going to use myself as the guinea pig. I'm an older woman. I won't tell you how old, but I'm very proud to be old, because it means that I'm alive and I've been surviving metastatic breast cancer. But let's say that I go to my clinician. And you probably know that in the States, there are very large hospital practices, there are smaller size practices of oncologists, and then there's some, one-person, two-team practices. So, let's say I go to a group that is two people. And I am suggested, a treatment is suggested to me that went through a clinical trial, obviously. And I say to the doctor, "Well, doctor I'm older now. I'm over 65. Tell me what was the experience of older people when they took this drug?" How would that doctor have access to real world evidence? So, my general question is, how do oncologists find out about what you are all doing?

JEREMY RASSON, MS, ScD, *Aetion:*
Yeah, it's a great question. And there's as always much work to be done in this area. High-quality, real-world evidence will be published in academic journals subject of course, to this same kinds of peer review as any other articles that they publish. And so, that is one major source of information for clinicians to understand the performance of medications in older populations, or other populations that either aren't specifically addressed in a clinical trial or are underrepresented in a clinical trial, like Renate was explaining. I think there are also other kinds of resources where those data are synthesized from journals presented as kind of medical reports that get shared with doctors at institutions, large and small. But I think dissemination of this information, dissemination of high-quality real-world evidence is something that we can always improve, and make sure that any clinician practicing in any kind of environment has access to that information for their own knowledge, and to be able to share with patients, and or like you were saying with the MBC connect, for patients to have the opportunity to understand themselves directly without kind of the filter, if you will, so that they can have the most informed conversations about treatment options that are available.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Thank you for that. And Renate, would you have any suggestions for someone like me who, let's say I asked my doctor, and well, I've had a couple patients who are over 65, and they seem to be doing well. Would you have any other sources? I mean, do I reach out to other people, other patients? What other suggestions would you give as a patient advocate?

RENATE HAIDINGER, *German Breast Cancer Association:*
Well, I mean, the best would be if there was one resource for all of these questions, which we don't have so far. But it would be nice to have something like that. But I think by now there are many, let's say, closed Facebook groups, for example, for patients that are taking a certain drug or medication. And they exchange. But the bad thing about them is that usually those can go into this group that have a lot of side effects and are struggling with the medication. So, if somebody wants to learn something, you can take the information that

certain side effects may come up, but it doesn't automatically mean that you will encounter these side effects. But they might help you out on how to overcome the side effects, for example. So, use them carefully. But I think that's at the moment, it's one of the best sources or to talk to your physicians. And also we, I mean, we collect all the data we get, and we try to at least give some advice, or hint for the patient if they ask us.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Thank you for that. That's very informative. Dr. Rassen, you talked about sources of real-world data being claims and billing activities, health records, et cetera. As a patient, I've always been told that my information is private, that I'm the only one with access to my electronic health record. Just there's that push and pull. I want to help with research because I want to live longer. Okay. And I want new discoveries. But then again, I'm thinking, wow, do I want to just give away what's happened to me? So, can you kind of, how does that all work out together?

JEREMY RASSON, MS, ScD, *Aetion:*
It's really important question. And maybe if you don't mind, there's a question in the chat as well that's related here, which is how do you guarantee the safety of the private medical information in the databases app. And thanks Lauren, for that question. And so, as you say, it's a push and pull. The way I look at it just as a researcher is, I have no need for in fact, I don't want any information that can be tied back to a specific individual. And what I'm looking for is sort of the larger experience across a group of patients, much more so than an individual's experience. And all the data that I work with are deidentified, which is similar to anonymized, meaning that I can't go back and take a piece of information that I have and link it back to a specific individual.

And in terms of how we guarantee safety of private medical information, so, de-identified information will go through a statistical review process where an expert in the field will go and make sure not only that there isn't names or things that are very specific identifiers of a patient, but also that the data isn't kind of so distinct that even if I didn't know a patient's name or birthdate or identification number something that I wouldn't be able to understand who they were because they live in a geography with very few people or have a disease that's incredibly rare. So, that's a statistical certification process that the data go through. So, that we're kind of insured as researchers that the data we're working with is at a de-identified level. And so, that I find to be very, very important. Publications based on that data, or other kinds of interactions say with regulatory agencies will also go through an ERB, an Ethics Review Board, to also ensure that as well.

And that's sort of the technical part of it, if you will, and sort of formal part of it. But that kind of aggregate experience that comes from a large medical record database for example, is just so valuable for understanding medications. You know the example of sort of a particular patient report on a particular website. That's a great place to start with a hypothesis of, well, patients are experiencing side effect X, Y, or Z. That's a hypothesis that we can then test and really see if that's a broad experience in the real world. And if it is, how do you counteract that, and what are some of remedies to that? That's what we can learn. And so, value of that broad scale information is incredibly high, and really helps us. A mentor of mine once said, the plural of anecdote is not evidence. But really helps us

understand sort of the plural of many anecdotes taken together, how those really help us understand the effectiveness of the treatment, and in the case of side effects or other things that are associated with it, how we can best identify those, and counteract those as necessary. Did that answer your question, Shirley?

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Yes. And I hope it answered the person who posted in the chat.

PATTI JEWELL, *Pfizer:*
Shirley, it's Patti. I just want to jump in here. Because Lauren did add on her question that it's her question is in the context of the MBC connect, I guess the database and app that you mentioned. So, if you can, can you talk a bit about how the MBC Alliance is working to protect patient's privacy?

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Yes. And that was something that we wanted to be very careful about. It's a de-identified database. The names are never divulged, nor are places where people live. The Alliance has people sign on, and then it is in encrypted, I think that's the correct word, their information, their identity is stored so that there is only one person from the Alliance that's been designated to have access to that. But if I was to go on and to look up a subtype and say, what patients have the subtype, there would be data that would emerge, but it would not have names attached. So, we want to be very careful with that. And nor do researchers who go into the database, they do not have access to names. So, we're very conscious of that. And we've never had any complaints. And it's been in effect, I want to say three years, a little more. I hope that answers Lauren's question.

PATTI JEWELL, *Pfizer:*
Thank you, Shirley. And I see another question in the chat also. Thank you Ranjit, for the question. She asked, is real world evidence practiced, reported, and evaluated in low- and middle-income countries? Perhaps Dr. Rassen, that's a question for you.

JEREMY RASSON, MS, ScD, *Aetion:*
So I agree. Thank you very much for the question, and it's a really important one. And I would say increasingly the answer is, yes. One of benefits of real-world data and real-world evidence is that there's essentially kind of no additional cost to collecting those data because it comes, as I mentioned from the routine operation, generally of the healthcare system. Insurance records will be created, medical records will be created for the reasons that they're created. But we can use them for the purposes of research as well. And so, while many of the real-world sources that we see today are from the United States and Western Europe, China, Taiwan, Japan, South Korea, increasingly also, we're seeing much, much more real-world data, real world evidence from Latin America, from Eastern Africa, from South Asia, from a lot of different parts of the world.

And again, sort of going back to the really important point that Renate made, that helps us get a much fuller picture of the medications. Because it's kind of the performance of a medication, the effectiveness of the medication is certainly about the medication itself, but it's also about the context in which it's given. And data from around the world in all

different kinds of countries, help us understand different contexts and how those medications perform within those contexts. And that's a really important part of what real world data and real-world evidence can help us understand. I hope that answered your question, Ranjit.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Dr. Rassen, you mentioned that the FDA was interested in real-world data and evidence, and we know that the FDA in the States is similar to the regulatory agency in Europe that approves drugs for use in the clinic, after a very thorough review of a clinical trial. What is the goal of that regulatory agency with regard to the real-world evidence that they would gather say from you and others? One of the concerns, I'll be very honest with you is, so let's say a drug that's been approved for use for whatever subtype shows that it's not very efficacious. I'm going to go back to the older woman I am. So, does that mean then the FDA would change their decision about who could use that drug? I mean, could this have a somewhat negative effect, or I guess you could look at it as a good effect also. I'll stop there.

JEREMY RASSON, MS, ScD, *Aetion:*
I think kind of negative or positive, and as you say that what you described could be looked at in one of two ways, right? It's either a medication that they may have had hope, it doesn't work in that particular subgroup, or it's the positive side of that is that that group is not taking a medication that's not going to be efficacious for them. So, it can different ways of looking at that. But I think broadly speaking in 2016, there was a policy enacted by the US Congress called the 21st century Cures Act. And part of the act, they call it Our Cures, is that real world data, real world evidence should be a more prominent part of regulatory process, for all the reasons that we've talked about today.

And so what FDA is doing right now is saying, okay, given that it's going to be a more prominent part of the regulatory process, these are our expectations of the quality of the data, of the presentation of the data, of how data are generated for our review. But I think there's even beyond what we've talked about so far today, there's a lot of uses for real world data. So, in many oncology trials, for example, you'll have a single arm trial, especially for rare diseases or for more advanced diseases, because there isn't the kind of a standard of care in some cases, in which to make a comparison. Real world data can provide that comparison.

So, we've seen many examples of what are called external control arms, where a single arm trial is performed, and the data are generated in a clinical trial setting like they would be in a randomized trial. But you can then draw patients from real world settings to represent that control experience. So, you get that in really important perspective of how much better a drug is, versus standard of care, or versus maybe even no treatment. And that can come from this combination of bringing the real world in the clinical settings together. And so, I think there are a lot of opportunities for regulators like FDA and EMA and PMDA and others, to understand relative performance of different treatment regimens. And I think that's a really important part of kind of the totality of understanding.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*

Thank you for that. And as I see the time is winding down, I really think that this opportunity for patients, no matter what their stage with breast cancer, can really contribute to research by sharing their data with their oncologists. If they are asked to share the data, they should really consider doing so, so that we know more about how people respond to a treatment in the real world as has been stated. So, I want to thank Dr. Rassen for his presentation, and Renate Haidinger for her presentation. And I'm going to turn this back now to Patti.

PATTI JEWELL, *Pfizer:*
Thank you so much, Shirley. And thank you, Dr. Rassen and Renate for your presentations and for the discussion. It was so very helpful to hear your insights and your expertise. There were a couple of questions with a theme of advocacy that we didn't quite get to. And I just wonder that perhaps this is how we close. And the questions are essentially, how can we get governments to accept real world evidence? And then how there shouldn't be so much burden on the patient, rather, our health system should be seeing this as important and be engaging more in this. So, how can we encourage governments and healthcare stakeholders to utilize real world evidence undertake this type of research and allow for this kind of learning to happen? So, Renate, I wonder if you have a closing comment on that, and then Dr. Rassen, if you're still available, I'll turn to you for the final word.

RENATE HAIDINGER, *German Breast Cancer Association:*
Yeah, Patti. I think it's at the moment, it's about having discussions and bigger rounds of payers of health insurances, and so on. What kind of data they expect to get and how, so that it gets more relevant, the real-world data and evidence for them to include in their decisions. So, I think that's in my view, it's at the moment, the point where we are to define what has to be done to make these data in a way that it can be accepted and included for decision makers.

PATTI JEWELL, *Pfizer:*
Thank you, Renate. Dr. Rassen?

JEREMY RASSON, MS, ScD, *Aetion:*
Yeah. And I agree with what Renate said. I think decision makers of all sorts, and I've talked a lot about regulatory decision making, but it's also payment decision making, which is a really important aspect for patients and for the system, are increasingly looking at these kinds of data as ways to make more informed decisions. And that of course includes clinical decision making, as well as what we talked about before. And that the data, because as I mentioned, they're coming from the healthcare system, there's minimal, I would be careful what I'm saying, because I want to be accurate about this, but sort of minimal kind of additional financial investment needed to create the data.

And I think very importantly, also the data are created as part of routine operations. So, you don't have to make sort of a proactive decision to create these data, they emerge. And that's a really useful thing A, for scale, and B, for completeness, but also C, if you have a question that emerges that you didn't sort of plan to answer with a particular data set, these given an opportunity to answer that question, even if you haven't specifically, say, collected a particular variable or specifically collected a particular piece of information and give the

opportunity to really go broader, especially if they're unexpected questions, then one could do with a standard kind of data set. So, there's really kind of a lot of opportunity here. And again, I thank you for the opportunity to talk about this, and for the opportunity to participate today.

PATTI JEWELL, *Pfizer:*
Well, thank you so much, Dr. Rassen, Renate, and Shirley for an insightful and inspiring conversation. We so appreciate your input. Look out for an email from me. We'll ask for feedback on this webinar and for future ones as well. Thank you so much for participating, everyone. We look forward to the next time. Take care.

SHIRLEY MERTZ, *Metastatic Breast Cancer:*
Thank you. Bye bye.