



COVID-19 Lessons Learned: Clinical Evaluation of Therapeutics

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Moderated by:

Susan C. Winckler, RPh, Esq., *Reagan-Udall Foundation for the FDA*
Kevin Bugin, PhD, *U.S. Food and Drug Administration &*
former Federal COVID-19 Response or Countermeasures Acceleration Groups

Susan C. Winckler: Hello and welcome to the Public Workshop on COVID-19 Lessons Learned: The Clinical Evaluation of Therapeutics.

I am Susan Winckler and have the privilege of serving as the chief executive officer of the Reagan-Udall Foundation for the FDA.

The FDA Foundation is pleased to host this important discussion to share information that's relevant today, but also helps us be better prepared [00:00:30] for the next public health emergency.

I'm going to open with just a few light housekeeping announcements. We have more than 1,000 people registered for today's workshop, and we are so pleased that each of you could join us. If you would like to ask our speakers a question, please post those in the Q&A function, and we will get to as many as we can. For those who submitted questions as part of the registration process, we have provided those to the panel moderators. Note, however [00:01:00] that none of today's speakers will be addressing any pending regulatory action, or answering any questions regarding such actions.

If we look at our agenda, you will see that we are scheduled to go from 1 until 5:30 and we have not scheduled a break. We fully expect that you may need to take one, and please do.

From a content perspective, Doctors Woodcock and Collins will get us started this afternoon, covering the landscape for the work thus far, looking back, [00:01:30] as well as providing a look forward.

We'll then, organize our discussion in three categories with a panel discussion of each. Looking at research scoping and prioritization, infrastructure and resourcing, and clinical trial execution.

Following the panels, we'll open the microphone for public comment to those who signed up in advance. We will call on registered commenters alphabetically, and we'll unmute your microphone, so that you may be heard. [00:02:00] Each speaker in the public comment period will be limited to 1 1/2 minutes. We will close your microphone at that 90 second mark.

Please note, that neither the FDA Foundation, nor the agency will respond to questions during that time period. And again, throughout the event, government employees will not comment on any pending, or other regulatory action.

With that, we can jump into the content because we have a lot of discussion to stimulate today. I'm going to turn the microphone [00:02:30] over to my co-moderator Dr. Kevin Bugin. He's, currently, the acting director of operations in Cedar's Office of New Drugs at FDA, but was formerly part of the Federal COVID-19 Response Team, which was also known as Operation Warp Speed.

Kevin, you've been instrumental in much of the work that we're going to discuss today. Would you provide us an introduction and prepare us for what we're about to cover in the next few hours?

Kevin Bugin:

Absolutely. Thank you, Susan. Really [00:03:00] appreciate the introduction, and really appreciate all the work that's gone into today's workshop, both from the Reagan-Udall Foundation for the FDA in organizing and getting us to this point today. I mean, it's really been a pleasure to work with you. But also to our panel members and, of course, our panel organizers who have also been working group leads throughout this entire initiative to gather the lessons learned, and generate some initial recommendations for how we might proceed within this current pandemic and future pandemic, or public health emergencies. And, of course, [00:03:30] I want to really thank all of our participants today. As you heard, we have more than 1,000 registered attendees. I do hope they'll join now throughout the day. And it's with your contributions that we'll really be able to achieve our goal today, which is quite simply expand the circle of the stakeholders who've been working with myself and Dr. Woodcock these past many months to share our lessons and recommendations on how to move forward with improvements. And also to get your input and your feedback. We really do value that.

And I want to just point out that there will be a [00:04:00] open... Or there is already an open docket that we can receive your comments, your questions. We've received several already prior to today. And I'm sure we'll receive more. And that docket will remain open for the rest of the year, I believe. And we'll be pulling in those comments at the end when the docket closes to sort of summarize and add those into the additional public discussion.

So, as Susan mentioned, what we'll be covering today is lessons and recommendations related to those three topic areas around how do we research, [00:04:30] scope, and prioritize the coordinated therapeutic

evaluation activities. And then, what's the necessary infrastructure and resourcing that's needed and really needed period. It's not something that you can develop during, or after the pandemic. You need it from the get go. You're either early, or you're late, and we simply cannot be late.

And lastly, then what's necessary for efficient and effective execution of clinical trials. In these three topic areas, we'll go through a number of some of those insights, and lessons learned, and potential recommendations that we've been generating with our panelists.

[00:05:00] So, as a reminder, why did we conduct this workshop? Well, the intent was really to provide an additional perspective and gather additional insights into this process of getting feedback on these lessons learned, and really disseminate these findings out across the entire public ecosystem, because we recognize we've been having great conversations, and a lot of convergence on many of these issues, but it's something that we need to take further.

So what's next? Well, as I mentioned, I think [00:05:30] already today is really a step in our journey. And what we're trying to do today is really talk about change. And change is never a one-time event, it's a continuous process. And to keep that process moving in the right direction, we need as much insight, and as many varieties of perspectives as possible.

I think as you'll hear from my colleague, Dr. Janet Woodcock in a moment, these lessons learned efforts that we've been in aged in is really a culmination of a series of those discussions and collaborative activities that have been occurring over the past many months, and really reflecting on that first [00:06:00] year of the pandemic. And what we'll try to do today is kind of just take stock of where we were, where we are, and where we're going.

So lastly, just a few reminders, there will be a recording of today's meeting. The slides, I believe are already available on the Reagan-Udall Foundation website, where you initially registered. We will also have a interim summary document that will build on the pre-read document, which is also already available on the RUF website. And that summary document will incorporate today's discussions. And lastly, as I mentioned earlier, as the docket closes later this year, we'll be summarizing [00:06:30] some of that public feedback as well to add into that ongoing discussion.

So lastly, with great honor and pleasure, let me go ahead and introduce someone who really needs no introduction, Dr. Janet Woodcock. So, please join me in welcoming our Acting Commissioner of Food and Drugs at the U.S. Food and Drug Administration. Hi, Janet.

Opening Keynote

Janet Woodcock, MD

Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration

Janet Woodcock: Hey, thanks, Kevin.

And hello everyone. I'm really happy to be talking about this. And could I have the first slide?

So, my task is to go back to the beginning and say, how [00:07:00] did we decide? How did we do what we did? And what did we learn as we did the things we did? So, I was the therapeutic lead for what was then called Operation Warp Speed. And it started with Kevin and me trying to figure out what to do. And so, I think we did, we gained a tremendous number of insights as we've moved along. And, of course, we worked with other components of the government. [00:07:30] You'll hear from Dr. Collins in a bit about how we joined up with ACTIV and were able to accomplish a great deal through that collaboration. Next slide.

So, it was established in May the Therapeutics Warp Speed Effort to try and pick out candidates, and then accelerate both their clinical development, and the scale-up of their manufacturing. [00:08:00] And so, it was sort of a crystal ball exercise to move forward and support those candidates that would most likely have a broad impact on the pandemic. And then, try to enable broad distribution and availability of these therapeutics until widespread access could be achieved.

And, in fact, it has turned out that we are still needing these. We knew there would be people who would not get vaccinated and people for whom the vaccine would not [00:08:30] be effective. And so, there would be an ongoing need, while the virus was still spreading around, for therapeutics. And we wanted to provide continued access for all of these across, no matter where you were, public access. And so, we decided to focus on candidates that attack the virus number one, particularly the monoclonals or small molecule antivirals, because [00:09:00] there was a huge effort going on with a lot of immunomodulators. And there a number of those were put in the portfolio, but it was hard to sort through those. And then, prevent or manage complications such as thrombosis, which was an early thing we worked on. And in January of '21 Operation Warp Speed was transitioned to the Federal COVID-19 Response, but continued to have the same mission. Next slide.

[00:09:30] So, this slide is probably hard to see, but the point of this is that we worked across many, many agencies and groups in the government, not only the HHS agencies, but DOD, Veterans Affairs, and many others to all work together. And this turned out to be very effective. We leaned on and had leads

of different therapeutic programs for many places around [00:10:00] the government. It was really extraordinary, I think. Next slide.

So, we learned a lot as we did all this, particularly about how one might clinically evaluate, bring forward and clinically evaluate therapeutics during the midst of a pandemic, and the insights were driven by much of the frustration [00:10:30] that all of us encountered in actually setting up and getting going, this clinical evaluation. And we were like starving in the midst of plenty. We had people ill in ICUs all over the country and yet, we couldn't enroll patients as fast as we really felt we should be able to do. And most of the patients were not put toward trials that could yield actionable [00:11:00] information.

So, we learned slower than we should have. And, in fact, manufacturing, of course, and making clinical supplies was also problematic, but there were tremendous barriers that it took many, many people thousands of hours to work through these. We think these insights can be applied to the broader clinical trial landscape in the United States, but improve our preparedness for the next public health [00:11:30] emergency, but also teach us more about how to more effectively have a learning healthcare system to actually rapidly evaluate interventions. So, there continues, of course, to be a public health emergency, but by 2021 it seemed like we didn't to just move on and lose those insights of those early days of tremendous struggle. And [00:12:00] so, from January to May, we collected and analyzed lessons learned from all these parties who had participated and more. Next slide, please.

So, over the course of the first half, we captured these lessons learned, we developed some recommendations and considerations for implementation. We did a huge number of interviews with many, many helpers that I'll get to in a minute. [00:12:30] And we got a 70 page fact-based document about all the different lessons learned in the documentation. Then, we synthesized that into 29 key lessons learned, and we had working groups and leadership who led these activities, and we had internal workshops, and meetings, and so forth. And then, we developed ways to address the recommendations, [00:13:00] and provide details, and references for implementation process that was really a starting point. Like, okay, if we're going to change this, what do we know now? What do we think? Where could we go from here? Next slide.

So, we formed working groups around these key topic areas. I have the leadership group, so it was across military, JPEO, [00:13:30] VA. We had a lead, we had VARNA involved, NIH and FDA. So, we had a huge span of people who were all working together. And then, we had leads from all the different groups shown below both the FNIH, FDA, and so forth and so on. All these people working together. And then, we had a lot of partners, external partners who helped [00:14:00] by collecting information from narrow organizations. For example, ACRO, which is the CRO organization. Bio and PhRMA, the biopharmaceutical and pharmaceutical industries. And then, a large number of other groups who helped us collect all this information and bring their point of view to bear as well. Next slide.

So then, [00:14:30] lessons learned were organized into five topic areas with four of those we're going to be discussing today. First one was, when Kevin and I started strategy governance and decision-making were extremely confusing to us. And how we feel that governance and coordination really needs to be set up in advance and so forth. [00:15:00] And that will be discussed in one group. Then, how do you pick among this myriad of candidates, and really do the scoping, and agent selection, and so forth evidence, generation, strategy and data sharing? We managed it and ACTIV had an agent selection group in BARDA and our therapeutics group had agent selection, but everyone was bombarded [00:15:30] with thousands of candidate agents, either those in development, or ones that wanted to be repurposed.

And figuring out a process even for working with all of these was complicated. And then, research on how do we compare similar agents, such as the monoclonals, of course, which many of them were against different epitopes, and how did they work against the various variants, and what [00:16:00] were their properties? And so, we worked with FDA and the Scripps Institute, and all sorts of parties, The Gates Foundation, and so forth, as well as NIH to try and get a handle on the properties of a number of these molecules that we finally ended up testing. Also, looking at animal models and their performance, and trying to do head-to-head studies in the animal models. So, [00:16:30] we had some comparative data to work from but, again, this was all back of the envelope. We did this as we went, there was no really game plan laid out for us to do this.

And then, infrastructure and resourcing, a lot of effort had to go in. ACTIV brought in a lot of the clinical trial networks and identified [00:17:00] a lot of the clinical trial networks that NIH had. But we really didn't have the clinical trial infrastructure that we needed to cover the United States. And we did struggle with diverse participation, partly because of where the sites were located. And the CRO infrastructure in the United States was, I think, pretty stressed by all the trials that were going on. [00:17:30] So, this was quite an issue.

And then, clinical trial execution, oh my goodness. This usually takes about 6 to 8 months or whatever to set up clinical trial in the government, or elsewhere even to get everything, all the sign-offs, everything that needed to be done. And we tried to accelerate that as quickly as possible, but there were tremendous barriers. [00:18:00] And then, we're not going to talk about supply distribution administration, but there are many lessons learned there as well. Next one, please.

And finally, in closing, many of the therapeutics lessons learned that we are going to discuss today can be found at a high level. I think in the recently shared presidents' pandemic preparedness plan, they call for strengthening the US public health system, investing in public [00:18:30] health labs, and digital infrastructure.

Another thing that we lacked was really being able to rapidly identify what variants were circulating in the United States and whether our agents we were developing would be active against them. A prioritization of vulnerable communities and making sure they're able to participate in clinical research, really important. And evidence-based communication, we did struggle. We struggled with getting publicity on the trials and also, getting [00:19:00] people to understand they needed to use the monoclonal antibodies, and that they could keep people out of the hospitals, and so forth.

Improve the regulatory capacity, platform technologies, for example, manufacturing so that you're not reinventing the wheel all the time. Clinical trial networks, if we had had ready to use networks that were more extensive and in the appropriate communities, [00:19:30] we could have been up and running much faster, had a much broader reach.

And then, improved regulatory capacity approaches at FDA. Of course, FDA did not have search capacity. It usually runs very close to the bone as far as staffing and so forth. And this caused huge increases in workload for the regulators. And then enhanced program management, which gets to what [00:20:00] I talked about at the beginning, the first item, decision rights, who's in charge, what are the structures for decisions, and so forth? And they call for enhanced program management mission control function, which would be very useful, and international coordination. Now, the FDA ran a lot of international coordination itself with drug regulators around the world but, obviously, there needed to be even broader coordination. [00:20:30] Next slide.

So, thank you very much. And I'll turn it back over to the moderators. This is just setting the stage, I think, for the questions.

Susan C. Winckler: Absolutely. And thank you so much, Dr. Woodcock.

I'm reminded, we certainly benefited from your, inimitable leadership style in scientific acumen throughout this public health emergency at Warp Speed. And no, at FDA.

I was [00:21:00] struck by two components in your overview that it's important to take time, even in the midst of an ongoing pandemic response effort to take a snapshot and dig into the issues, and come up with recommendations before our memory and the information changes too quickly. And then, as well, struck by the all of government and private sector engagement in the effort to aspire to make sure that the collaborative work was collaboratively reviewed. [00:21:30] And then, finally, that we have some of this being implemented today to adapt our ongoing response. Is that fair?

Janet Woodcock: I think that's all fair. I mean, it was really breathtaking, the extent of collaboration across all the sectors. I would credit Kevin Bugin for the idea that we really need to do lessons learned quickly because, of course, he was always

in the middle of all these administrative problems and how we're going to solve them. [00:22:00] Yes, but it was really spectacular, the collaboration across all the sectors. And I think it was a selling that everyone put down their parochial needs and so forth and put their shoulder to the wheel. So, it was a very positive experience in that way, but it would have benefited from more clarity of this mission control's a very good idea in other words, yeah.

Susan C. Winckler: Yeah, definitely. [00:22:30] Well, appreciate that. And we'll look forward to hearing you back on panel number one.

But I will go ahead and take us to our second opening speaker. And this is where we will hear from Director of the National Institutes of Health, Dr. Francis Collins. And you've been, similarly, quite involved in all of these efforts. And I know that you have a presentation also to walk us through. I'm going to get out of the way and turn the microphone over to you. Thank you, Dr. Collins for joining us today.

Opening Keynote

Francis S. Collins, MD, PhD
Director
National Institutes of Health

Francis S. Collins: [00:23:00] Well, thank-

(silence).

[00:23:30] Well thanks very much for kind words, Susan. And thanks to Kevin for all the hard work in prepping us for today's workshop. But special, thanks to Janet Woodcock, who's just been a fantastic partner as we have struggled through these last 21 months of the worst pandemic in more than a 100 years, trying to steer our agencies in the direction that would do the most good [00:24:00] to try to help the public. And Janet has been tireless, wise and extremely capable in her management of FDA. And there have been many times where she and I have had to communicate at strange hours to try to figure out how to make the system work. And she has never failed to come forward with a creative solution. So, Janet, it's been terrific being your partner through this. And now we can partner in figuring out what the lessons are and how to learn from them.

And I thought, I would say a little bit [00:24:30] about that as sort of, again, a bit of a queuing up of the panels who are going to dig more deeply into all of these issues. And it's a great group of people on those panels. So, I'm looking forward to hearing what they think about all of this.

You ended with a remark about the president's pandemic preparedness plan coming from the White House, just this month. A bold one, shall we say with a bold price tag, but let's admit [00:25:00] that if we're really serious about preparing for the next pandemic, while we're still trying to finish dealing with this one, it's going to take resources.

What's in that plan, which is well worth your careful perusal, are these five different areas that you see listed here on the slide. But most of what we're talking about today relates to that first one, transforming medical defenses through vaccines, therapeutics, and diagnostics. But none of that works if we don't achieve goals in the other [00:25:30] places as well, the public health systems, the situational awareness for monitoring, the core capabilities we need. And yes, mission control. A way in which those can all be managed in an effective, seamless way, including our international connections. So, again, if you want more details about that, I would refer you to the actual document. A lot of work went into the ideas that are put forward there that we are, certainly, enthusiastic about seeing the implementation.

[00:26:00] But I want to reflect a bit on COVID-19 initiatives that NIH had a particularly heavy role in, although all of these ended up only being successful because of partnerships. There are five here that I could go on about, and I will speak at least a little bit about each of them, except I won't talk about RADx, the second one, which is about diagnostics, because our real focus today is on therapeutics and their clinical testing.

But let me walk you through [00:26:30] some of those experiences beginning with ACTIV, which Janet has already mentioned, in which FDA and Janet herself was a very significant part of. Turn the clock back to March of 2020, and survey what's happening at that point in terms of therapeutics for this rapidly spreading worldwide pandemic caused by SARS-CoV-2. As I looked across that landscape and saw the efforts that were being made, all very well [00:27:00] intentioned in therapeutics, it was scattershot. In fact, I think we used that word regularly when looking at that landscape.

There were many, many small scale trials that were sort of based upon a hopeful view that repurposing of some compound that might potentially have value oftentimes, based on fairly shaky data. And it might just turn out to be the thing that would save lives, as lives were rapidly being challenged [00:27:30] by COVID-19.

Many of those trials were too small to have any real chance of having a meaningful result. They often were not particularly well-designed as far as what the end points were. And a vast number of them were working on the same thing, hydroxychloroquine, without really working together to try to build what would be a more definitive trial. There was also a big effort on convalescent plasma, but not organized as a randomized control, but as an open label effort which, in retrospect, [00:28:00] is really unfortunate that we didn't manage to get that off on the right foot.

Looking at this, talking to Janet, talking to my colleagues in academia and in industry, we all came to the conclusion, this is not the way we are going to tackle this terrible threat to our country, to our planet. And so, in April, by pulling together very quickly partners across multiple agencies and very explicitly reaching out to our colleagues in industry, [00:28:30] we launched ACTIV, Accelerating COVID-19 Therapeutic Interventions and Vaccines, public-private partnership, an unprecedented one, to try, as you can see from the mission here, to really collaborate on prioritizing the therapeutic candidates that needed to be evaluated, and to do so rigorously. To come up with clinical trial capabilities, coordinate the regulatory process, do all of that, and do it at a pace that had not previously been necessary [00:29:00] but now, certainly, was.

The stakeholders, now that ACTIV has been around for a year and a half, and it's still very much involved in this, we'll have our next leadership team meeting of ACTIV day after tomorrow. And it is populated not by people far down in the organizations but, in many instances, by the heads of the organizations that you see here or their deputies. 20 companies now taking part in ACTIV. Eight government agencies, [00:29:30] as you can see here, nonprofits and, very importantly, with program management provided by the foundation for NIH, with their remarkable skill sets there. And you'll hear about that from a couple of those Stacey Adam, and Mike Santos in the first panel who are part of the program management capabilities that FNIH brought to this ACTIV issue. Stacy for therapeutics, Mike for vaccines.

ACTIV did get involved in vaccines [00:30:00] by playing a significant role in the design of the master protocol. So, when you notice that most of the vaccines that have gotten rigorous testing have tended to follow the same protocol in terms of what the end points were, and the size of the study and so on, well that's because that's how ACTIV, working with industry partners and FDA, designed this as the way to get the answer you could trust. And I can't say enough about how critical it was that FDA was at the table in all of these master protocol plans, so that we knew [00:30:30] we had something that would stand up to intense regulatory oversight.

ACTIV broke up into four different subgroups, preclinical, therapeutics clinical, clinical trial capacity, and vaccines. The therapeutics clinical, maybe is the one I'll focus on most here, given that we don't have a lot of time. One of their tasks was to look at this landscape of possible therapeutic agents, and try to prioritize which of those ought to most [00:31:00] quickly get into rigorous randomized controlled trials. We started with about 600 of those, and they had to be looked at, each one of them to see what was the evidence, and the likelihood that they could be successful. And that meant what's the scientific basis of the claim for benefit, but also something more practical, like suppose it works, is there a manufacturing plan about how you could actually develop a supply chain and provide this to people if you had a successful outcome? They went through [00:31:30] all of that prioritizing starting with hundreds, coming down to dozens. And, ultimately, we've now tested more than 20 different therapeutic

agents as part of ACTIV master protocols, and the therapeutics clinical group also designed those master protocols. So, they were pretty busy.

Clinical trial capacity group faced with, "Okay, how do we actually do this," looked at all of those trial networks, some run by NIH, some by industry, some of course in CROs, and tried [00:32:00] to imagine how you could take this very disparate group of trial networks, many focused on something other than infectious disease, and ask them to get ready in a matter of weeks to begin enrolling patients in a master protocol that maybe they didn't design, but was going to be handed to them with the request to run it just like this. And that happened in a way that was, at times, bumpy along the road, but enormously willingness was encountered on the part of all those who [00:32:30] had to drop everything to take part in this, and they did so.

I think we did learn is that it would have been good if we'd had such a national, let's say, international clinical trial network that was being kept warm all the time to take on a public health emergency like this. We didn't have that. We had to kind of create it, and that was not easy. But, again, the willingness of people to go in a new direction was remarkable.

So, what came out of that? Here are the six master protocols, [00:33:00] 1 through 6, although some of them have subsets, I'm not going to...

PART 1 OF 4 ENDS [00:33:04]

Francis S. Collins: The calls one through six, although some of them have subsets. I'm not going to walk you through much. You can see just in terms of the compounds that are listed here, the therapeutics, those that are in green were shown to have efficacy in randomized controlled trials. The ones in red failed, basically. They were given up because of futility. It's also good to know when something doesn't work and then the others that are in neither color that are in white are currently ongoing. So we're still [00:33:30] very much in the middle of this. This morning, the war room, [inaudible 00:33:34] as we do regularly. And we looked at the list of meetings of active working groups this week. I think there were 32 of them just this week. So this is a very ongoing, intense effort. So what did we learn about this? Well, we also did learn things that don't work.

And as I mentioned, that's extremely important to have that list. We know that the things that you see here are probably not going to be [00:34:00] things that should be propagated. One of the surprises, I'll just point to the next to last one is that monoclonal antibodies, despite our best hopes that they would be the way we could rescue people who are really sick in the hospital with COVID-19, they all kind of failed in inpatient trials. And I think the reason for that is by that point, the patient's immune system had already generated their own antibodies and adding additional ones apparently was not really going to make that much difference where monoclonals worked with an outpatient [00:34:30] shortly after diagnosis. And there many lives have been saved by access to those, even though the awkwardness of the delivery because it has to be intravenous or

occasionally intramuscular made it more difficult to actually come up with a way in our medical care system to readily do so.

If I had to summarize sort of the big picture then of what we learned about therapeutics for COVID-19 from all of this, it's that antiviral strategies [00:35:00] like monoclonals work best early on. And we think that's probably going to be true for small molecule antivirals as well, which I'll come to in a second. Whereas immunomodulatory strategies, dexamethazone being the most dramatic, but there are others also that have showed promise here seem not to be the thing you'd want to give early on. You want your immune system to be working hard at that point. But by the time somebody is in the ICU, their problem at that point is more overreaction of the immune system than [00:35:30] it is ongoing viral infection. And they are immunomodulation can in fact be important and can save lives. Anticoagulation has been really interesting because we did learn early on that this virus is quite capable of promoting thrombosis in small vessels and anticoagulants therefore seemed to be a really good idea.

What we do know is that they do provide benefit early in hospitalized patients, but not later on after organ failure has happened. So you have to be very selective [00:36:00] about exactly how and when you administer that kind of therapy. We never would have figured that out without the rigorous trials, in that case carried out in active form. What about antivirals? Many of us would have hoped a year ago to have a whole menu of very targeted, small molecule antivirals directed against some weak spot in SARS CoV-2's ability to replicate itself. We didn't [00:36:30] have those. So everything was done in those active protocols to repurpose compounds that have been developed for other reasons, hoping that they would work in this regard. And we had, to use a baseball analogy, a single or a double here and there, but we didn't have any home runs. And what we need now are the home runs.

And so the APP, which is now underway funded by the American Rescue Plan, aims to do that working between NIH, academia and industry to basically build a sustainable platform [00:37:00] to discover new antiviral, starting with COVID-19, but ultimately with other potential pathogens as well, bringing together experts into these multidisciplinary discovery groups called AViDD centers and using both drug design by structural principles and also high throughput screens with various assays to find compounds that have promise. Many of them focused on the proteases that the virus needs in order to process itself in which are virally [00:37:30] encoded. So if you attack those, you should have both efficacy and low toxicity. All of that is planned in the APP which is now vigorously underway, but has not yielded the kind of immediate fruit that we wish we'd had a year ago.

This is a quick diagram of the Corona virus life cycle. Just to say, there are a number of places here where a small molecule could be quite effective in terms of blocking replication and the protease inhibitors [00:38:00] are the moment, the favorite one, along with polymerase inhibitors that are also being pursued.

A little lesson here for the future. If we already know a list of perhaps the 20 most likely potential pandemic pathogens that might be lurking out there waiting for us, maybe we should start now to develop those small molecule antivirals, especially those that are potent enough to affect an entire class of viruses, not just a specific one. And [00:38:30] then we'd be a lot further along preparing for that next pandemic. And that is in fact, part of the plan that I started off mentioning that the White House has put forward to deal with pandemic future.

One other thing to mention in terms of something that ACTIV was able to put together and now has become a very prominent part of what we're doing is to track the development of in SARS CoV-2 that [00:39:00] carry significance both in terms of how they transmit, how contagious they are, but especially how they affect therapeutics, monoclonal antibodies, vaccines as well. And certainly you want to have a systematic way of tracking those and pulling together as quickly as possible, the assay's of how they affect function of therapeutics and the vaccines. That's what TRACE is now doing. And it's helpful because industry is part of this. And [00:39:30] of course they're intensely interested in functional consequences of these variants of things like Delta and [inaudible 00:39:36]. All of that is now being held together in a component of ACTIV called TRACE, which has open database where you can go and find a lot of information about what we know about all of the variants that are currently circulating.

And then another really important issue, before I come to conclusions, was the concern about whether in the clinical trials that need to be done, are [00:40:00] we successfully reaching out to the groups that have been hit hardest with COVID-19? We all know that this pandemic has shown a bright and very troubling light on health disparities and that groups that already were not being well cared for in our health system were shouldering a burden of this disease in terms of hospitalizations and deaths that was sometimes two or three times greater than the more privileged groups. And so if we were going to run clinical trials [00:40:30] to see if therapeutics or vaccines are working, you want to be sure you are inclusive of participation. For that effort, we mounted over a year ago, something called CEAL, the NIH Community Engagement Alliance, recognizing that running clinical trials when the management comes from the top, maybe somewhere far away, it's not necessarily the way you win the trust of communities to take part in those trials.

You really want people on the ground who know those communities, who have an understanding [00:41:00] of their concerns to be your partners. And that's what CEAL has tried to do now in more than 20 states, as you can see at the bottom, figuring out how best to tap into those experts, those knowledgeable members of the community, to help us as we do that outreach. And I think what you saw happen, particularly with the vaccine trials, when a very short order you wanted to get 30,000 participants and to have the representation be something similar to our country, we started [00:41:30] out way behind on that and with a big push from CEAL and making this a high priority, not just a nice

thing to have, many of those achieved 35, 40% racial and ethnic minorities. And we ought to set that as a goal going forward for all of our clinical trials. |.

CEAL could help with that, but there's lots of other efforts in this space as well. So to conclude, I think it's fair to say we have made substantial and progress in prioritizing and testing therapeutics. That was something that [00:42:00] was missing in April of 2020 and rapidly got pulled together. And it was remarkable to have people willing to drop everything active with those four working groups, more than a hundred people who pretty much 24/7 were devoted to this effort. And that was a lot of intense work to try to set those priorities for therapeutics. And we were working against, as I pointed out in the second bullet here, well-intentioned but poorly designed and underpowered trials that [00:42:30] were wasting a lot of our clinical trial capacity. We have learned a lesson there and NIH is a main funder of some of the infrastructure that supports academic medical centers. We have a role to play here, I think to try to be sure that that lesson gets learned.

And we don't, once again, in the future, not find so much of our energies being extended in ways that are unlikely to provide the kind of data that's going to change the course of an illness. We did, as I showed you through [00:43:00] these master protocols and clinical trial networks and prioritizing therapeutics find multiple therapies that have been beneficial, particularly monoclonals, and a lot of others that had no value. And it was good to know that too. The repurposing of existing drugs, you'll always want to try that, but you can't expect that necessarily to be the answer. So as soon as possible, developing and testing targeted drugs that are really focused on the pathogen. And I didn't mention this, but it's certainly likely, [00:43:30] even if we do get good antivirals, that they may need to be used in combination to have full effect and not to have resistance rapidly develop, remember what happens with HIV?

This is a different virus, but the same principle could apply. And then the many lessons. For me, having been pretty much a hundred hours a week devoted to COVID-19 for the last 20 months. The only way we got to where we are is because of these partnerships, the willingness of people really to [00:44:00] ignore previous senses about boundaries and to recognize what can we do together that is going to advance the cause of public health? And it was wonderful to have that opportunity more broadly shared, not worry too much about who's going to get the credit and figure out how to do this in a way that was going to be rigorous. It would be something you could really trust and believe the results. And that's a lesson that we learned, but we could have done it a lot faster if we'd been expecting that something like this might be necessary.

So please, [00:44:30] as we hope to see, COVID-19 eventually in the rear view mirror, let's not forget the lessons learned. That's what we're here to talk about today. Let's try to have a different view than we have often had in the past where we go from panic to complacency. Complacency is not our friend. Here we really need to think through how to have all the pieces together and to do as much work in anticipation of what that next pandemic is before it hits us,

because it's going [00:45:00] to. I don't know anybody who would say, oh, don't worry, that was the last global pandemic, we're done with those. We're not going to be that lucky. So thanks very much. Glad to had to have a chance to share those few thoughts with you and looking forward to the panels.

Kevin Bugin:

Thank you, Dr. Collins, that was a fantastic opening and closing to our keynote and it really hits home. I think the point you make around collaboration and that we essentially dropped everything else and were able to come around to this unifying problem [00:45:30] and really work together. And I think we need to somehow not forget that as we move forward and hopefully put this pandemic in the rear view mirror.

So thank you again for making that point. So with that, we are right on time to move into our first panel, which will be on research scoping and prioritization as introduced by Dr. Collins, we will be welcoming our moderators for this panel, Dr. Stacey Adam, who is from the Foundation for the National Institutes of Health and Dr. Michael Santos also [00:46:00] from the Foundation for the National Institutes of Health, both were actively involved in the active partnership that we just heard about and will be walking us through sort of the lessons learned around how you set a research agenda and prioritize on an ongoing basis some of the activities that Dr. Collins also just mentioned. So I will jump off camera and turn it over to both of you. Thank you all.

Panel 1: Research, Scoping, & Prioritization

Moderated by

Stacey Adam, PhD

Foundation for the National Institutes of Health

Michael Santos, PhD

Foundation for the National Institutes of Health

Panelists

Janet Woodcock, MD

U.S. Food and Drug Administration

Phyllis Arthur, MBA

BIO

Elliott Levy, MD

COVID R&D Consortium

Sarah Read, MD

National Institute of Allergy and Infectious Diseases

*Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Therapeutics-Clinical Work Group
Co-Chair*

Michael Santos:

Great. Thanks so much, Kevin. So hello [00:46:30] everyone. I'm Mike Santos, my colleague, Stacey Adam and I work at the Foundation for the National Institutes of Health and had the great opportunity to facilitate the research scoping and prioritization working group of this initiative. Before we begin with the panel discussion, I'll give a very brief overview of the results from the working group. So the working group was focused on how the clinical evaluation of COVID therapeutics was organized. For example, how the different disease stages were considered and how Canada treatments were prioritized for clinical [00:47:00] evaluation. It also covered how trials were designed, such as efforts to develop master protocols, [inaudible 00:47:06] endpoints and planned platform trials. We also consider the communication and coordination across the many groups with a stake in this endeavor. If you haven't already, you can read more about the context and the process for the working group in the meeting pre-read.

And so next I'll briefly summarize our main findings. So one key cross [00:47:30] cutting message was the importance of preparation, which is something that Janet and Francis both touched on in their opening comments as well. So the groundwork for response to a public health emergency has to be laid ahead of time. The research response will begin immediately whether or not structured scoping and prioritization has taken place. So the earlier those functions are ready, the more effectively they will be able to coordinate an efficient and effective collective research response. [00:48:00] So this slide... If I could have up the recommendations slide, please... Shows the main recommendations from the working group. So the first is the importance of learning about the pathogen and the disease as quickly as possible and sharing that information so that it informs research plans. The second is to foster the creation of actionable evidence by the clinical trial ecosystem.

So that is ensuring that studies have the best designs for answering key questions [00:48:30] about therapeutics. And that's another topic that you heard both Canada and France has really emphasized the challenges that have been experienced so far and the importance of being able to address those prospectively for future public health emergencies. The third recommendation is to enable sharing of research strategies and plans. And I think something we experienced in this emergency is that coordination depends on knowing plans, not just announced activities and the speed of the [00:49:00] response demands that you have to be able to talk about what you're thinking about, not just what you're doing. The final recommendation again emphasizes the importance of timely information to inform research, feeding back data from trials and other studies as quickly as possible to inform plans going forward. There's more detail on each of these recommendations in the pre-read document, but right now we're delighted to have a great panel assembled to share their perspectives on the lessons learned and recommendations [00:49:30] going forward. I'll hand the session over to Stacey to introduce them and get the conversation started. Thank you.

Stacey Adam:

Thanks Mike. Yes, it's my pleasure today to be able to introduce our four panelists for this first session. The first being Dr. Janet Woodcock, the acting commissioner of the USFDA. Phyllis Arthur, the Vice President of Infectious Disease and Emerging Science Policy from Bio. Dr. Elliott Levy, who has been working with the COVID R&D consortium, and is helping to [00:50:00] lead the new Intrepid efforts. And Dr. Sarah Read, who is the Deputy Director of the Division of Aids at the National Institutes of Allergy and Infectious Disease, and was the co-chair for the active clinical therapeutics working group.

So with that short introduction, because I want to leave a lot of time for discussion with our panel, we are going to just jump right in. I am going to take moderator's prerogative to sort of get us kicked off and move forward. I'm going to start with a question that I'm going to address first, both to [00:50:30] Sarah and Elliot and Sarah I'll have you go first and Elliot we'll have you go second, but we'd like you guys to briefly describe kind of the efforts that you were involved with, how did or does research scoping and prioritization really happened for those COVID therapeutics? What was the process that both groups took to kind of get to the place where you were able to get agents into trials?

Sarah Read:

Sure. Happy to start. Thank you, Stacey and thank you, Mike and Stacy for inviting me to participate in this panel and [00:51:00] also for your leadership in this exercise of identifying lessons learned in research scoping and prioritization. As Dr. Collins described earlier, one of the four working groups of the active public private partnership was the clinical therapeutics working group. And we had two main mandates, which were to prioritize agents to go into master protocols and to design those master protocols. And I'll start by just saying [00:51:30] that we had a phenomenal group of participants in our working group who worked day and night literally to get us started and have continued to to this day to make sure that the trials that we've designed continue to be implemented, but it really was an amazing group effort that included not only the original participants that you saw in the leadership group of ACTIV, but many additional partners that we brought in along the way, including a number of academic [00:52:00] investigators as well.

So just to briefly describe the agent prioritization activities, as Janet mentioned, we really learned as we were doing it, we were really under tremendous time pressure, rightly so, to get to answers. So we made decisions for better, for worse and acted on them and then acted iteratively to refine them as we kept going. But initially we came up with what we thought were [00:52:30] some key sets of triage criteria as well as scoring criteria. And that's how we systematically were able to evaluate hundreds of agents, as Dr. Collins mentioned, that we were able to access early on and as he mentioned, really what we were starting with was looking at repurposed agents. We didn't have a number of novel antivirals we could pull off the shelf. So we took what was publicly available about hundreds of potential candidates, and then had to systematically [00:53:00] apply these criteria that we came up with.

And we did that as I mentioned iteratively through several waves and as we progressed, we not only refined our criteria, but we also learned more about COVID and were able to apply what we learned about the pathogenesis of the disease to our process. We brought in additional expertise as we felt it was needed. We came up with additional sets of criteria for specific types of interventions. For example, for the [00:53:30] broadly neutralizing antibodies, we came up with a different set of criteria that were more, a minimum set of criteria that had to be met as opposed to criteria on which we would prioritize. And we had an additional set of criteria more recently that we've put together to look at repurposed agents that could be used in a remote designed trial. So it really has been an ongoing process that has been refined [00:54:00] as we go along and as we learn more and as we identify additional needs.

And then on the master protocol side, so this is going on in parallel, but in communication with the agent prioritization group, we started out with the idea that we were going to design a master protocol for evaluating agents that got prioritized and through making a set of strategic decisions quickly came to the conclusion that one master protocol, although it might've been possible to design, really wasn't going to be the most [00:54:30] efficient way to answer all the questions we wanted to ask about treating COVID.

So we initially discussed where in the sort of spectrum of disease we thought it would be most important to intervene and started by saying that would be with hospitalized participants. And that's how we designed our first protocol focused on that patient population. But we knew right from the beginning that that was not going to be the only question to be asked. We wanted to also look at those patients [00:55:00] who had mild disease and were not yet hospitalized.

We wanted to look at the other end of the spectrum of participants who are very sick and in the ICU. And so we developed a number of master protocols to focus on those different patient populations. And then we also designed different types of master protocols to look at different types of interventions, whether it was looking at immunomodulatory agents was our first set [00:55:30] of repurposed agents that got prioritized or more specifically to broadly neutralizing antibodies and also repurposed antiviral agents. And then more recently we've been looking at agents specifically for those with end organ failure in ARDS in the ICU. So we made a set of these strategic decisions about what types of master protocols would be needed. And in addition, from there, we made strategic decisions about the types of design issues [00:56:00] we wanted to address. And as Janet mentioned, really critical, an overarching philosophy, I'd say to all the master protocols is that we wanted to have the resulting data be clinically actionable results.

So we wanted to design rigorous clinical trials that would ultimately, if successful if the agents were proved to be efficacious, good results in an EUA. So that was an overarching principle. And [00:56:30] to get there, we made a series of additional decisions such as that we wanted a placebo control for each of the trials. And these were really just critical decisions that we made along the

way. And we can debate whether they were the right ones or not, but those were our guiding principles. We made some more detailed decisions that we were going to compare each agent against the control, not against each other and so on and so forth. And again, we've iterated on those decisions as we've gone forward. Of course, now we have effective therapies in the outpatient setting, for example, [00:57:00] and so we've pivoted to a non-inferiority type design where we have an active control, but those are the types of decisions that we were faced with and made along the way in developing this master protocol.

And so I'll say that in summary that we have taken the time, I agree that it's really important to reflect back on lessons learned thus far and within each of these work streams, the agent prioritization and the master protocols, we have taken time to document [00:57:30] our processes and our decisions. And those are now available in, I believe they're both online available in critical care medicine, the agent prioritization deliberations, and then the master protocol processes in Annals of Internal Medicine. And I hope that it will be helpful in the situation where we would have future pandemics, but at the very least to look at the questions that we had to ask ourselves so that we weren't asking them as we went. Ideally [00:58:00] you would know the types of considerations that you would have to make upfront. You have a roadmap, so to speak, even if there might be some nuances to the situation. But I guess I'll stop there and say that those were our sort of overarching approaches to agent prioritization and master protocol [inaudible 00:58:21].

Stacey Adam: Thanks, Sarah. Elliot, do you want to add onto that [inaudible 00:58:27] how COVID R&D maybe did it a little bit different or [00:58:30] lessons that you all learned?

Elliott Levy: Well, I think we did it more like than different, but I'll just maybe take a moment for those who don't know to describe the COVID R&D Alliance, which launched in March of 2020 under the leadership of the heads of R&D at [inaudible 00:58:46] in Bristol. It self-assembled. Ultimately, there were over 20 members, including most of the largest pharmaceutical companies, small biotech consultancies venture [00:59:00] and communications firms. And the Alliance had three principle R&D activities. It ran a screening platform for compounds that were in industry refrigerators and ultimately screened over 3000 of these compounds and identified a number that were identified for progression. It launched a real-world data stream where the companies pooled their data resources and analytic [00:59:30] resources to develop standards and methods that were used to rapidly develop essentially information on incidents, clinical presentation, clinical course, and outcomes in COVID-19.

And then I think what we're most interested in today was the clinical therapeutics work stream. And we had the same challenge to identify high priority compounds. I think we started off with a much smaller pool than ACTIV did. We focused [01:00:00] only on those agents that were manufactured by companies that were in the Alliance. And each company conducted its own

internal prioritization. So we started off with the list of about 30 candidates rather than over 500, but ultimately we prioritize them in very much the same way ACTIV did. In fact, I think ACTIV should be commended for developing quite rigorous procedures for screening. We used [01:00:30] essentially the same scientific criteria based on mechanism of action, available preclinical and clinical data safety database, the PK in metabolism [inaudible 01:00:44] drugs and then factors which would determine their ultimate value of the medicine, including its availability at scale and ease of manufacturing.

So, we went through the same process, [01:01:00] actively supported the launch of platform trials, where our agents could be tested. And we launched what I think is, to my knowledge, is the first industry multi-company platform trial, where ultimately three of our highest priority agents were tested. One of them determined to be futile, which again is a value. So I'm not going to say more because I think we should leave time for questions, [01:01:30] but I just want to reiterate that I think we're in violent agreement with the active group on how we can best identify these agents. It's the pragmatics of sifting through large numbers of candidates that was perhaps the greatest challenge.

Stacey Adam:

Thanks, Elliot. Yeah. We'll definitely get back around to doing some further questions on that one. I want to take the chance to pull both Janet and Phyllis into the discussion now. [01:02:00] Janet, I know in your intro, you talked a little bit about challenges, small trials and things that we face there. I was wondering if you might want to just deep dive on that a bit more about when did we start seeing these, how did we attempt to start addressing that sort of thing and really what you saw around just the sheer balloon of trials ongoing?

Janet Woodcock:

Well, everyone leaped into the fray and tried to help I think when COVID started [01:02:30] spreading around the world. And so investigators and seemed like every medical center and other places started their own series or started to do a small trial or joined up with other people. And of course these were all repurposed agents and we did a survey, Kevin and I commissioned this and now it's [inaudible 01:02:53] I think, by NCATS this information of all the registered trials around the world, in the United [01:03:00] States. And basically what we found is fewer than say astonishing percentage, maybe fewer than 5% or 5% or fewer of the actual trials were adequately designed and powered to yield actionable information. And many of them were duplicative, as already been said by Francis, they studied the same thing over and over, but in too small of trial to actually yield information.

And the [01:03:30] same thing happened with the convalescent plasma trials. And these were agents that were fairly easy to obtain. And so when larger trials started to get run, patients had been sucked up and clinical research staff had been sucked up by these other trials that were ongoing. Well, this was true around the world and true in the United States as well. And Stacey, I wanted [01:04:00] to say one other thing about what's been said already, if I may, when Sarah was talking about, one of the problems with sort of not this master control at the top sort of thing was active, was looking at agents and they were

promising agents, but then of course BARDA was working on, can they get manufactured? And you know Stacey how much you struggled to help companies get to the point where they could even make clinical supplies that would be adequate and make a placebo, [01:04:30] right?

And these are the things that aren't really talked about, but you have to have a placebo if you're going to do a placebo controlled trial. Somebody has to make the placebo and it can't take six months to do it. And so BARDA was doing some of the clearing the way trying to get the supplies, but they had their own prioritization process and the contract mechanisms that they used and so forth to do those things.

[01:05:00] And that was kind of different than what ACTIV was doing in some ways. And so in the future, I would hope we'd have a very unified... We all tried to unify that as much as we could, but there were tremendous struggles that we haven't talked about around the placebos, around the clinical supplies and Stacey, at least, because I worked with Stacey on this, I don't know about the vaccine side, but Stacey was just a hero in all of this and [01:05:30] very patient, but we had lots of candidates that people wanted to put forward that simply couldn't be tested. They didn't even enough supplies to test it in a large scale clinical trial, much less than be able to provide it to the population were useful. So these were other practical considerations that we struggled with the entire time.

Stacey Adam: Yeah. And actually, I think that's a very nice segue into what I was going to ask [01:06:00] Phyllis. So Phyllis, obviously Bio oversees smaller...

PART 2 OF 4 ENDS [01:06:04]

Stacey Adam: So, Phyllis, obviously, Bio oversees kind of smaller contingent companies, and you just heard Janet sort of articulate some of the challenges that were faced. I was wondering, could you elaborate a bit on that?

Phyllis Arthur: No, it's wonderful, actually, to have Janet Woodcock actually say what I was thinking in my head. I feel like I'm in great company. I think that, in essence, that's what we saw as well when I look at the recommendations we're going to discuss. A lot of them capture the frustration of small and midsize companies. So, what you saw in those first couple of months, [01:06:30] once we had the sequence and people started to understand the natural history, was hundreds of companies of all sizes, investigating the products they had in pipeline, regardless of what phase they were in for their ability to help solve something along the continuum of treating or preventing COVID-19.

And in a therapeutic space, I think, because the topic was so broad, in the vaccine space, relatively straightforward, can you prevent severe disease and hopefully transmission [01:07:00] with a vaccine? In the therapeutic space where you're trying to do early stage disease, mid stage disease, late stage. I

think there were a lot of companies that were very interested in bringing products forward that had, what I'll call biologic plausibility, but they didn't fit in to what I thought were the very clear strategic goals that Janet and Monsef laid out about operation more speed was, "What can I have right now?" Right?

And I think that companies understood that there was a need to quickly operationalize around products that were near-term, late-stage, [01:07:30] manufacturing is already clear. Maybe they were already existing or they were in late stage and they could help us right this minute. Where we, I think, had a hard time figuring out how to plug in was those companies with things that could be breakthrough in the treatment continuum. And where did those products go? Did they go to Barta? Did they go to DOD? Did they come to Active? And how did they get assessed?

And I remember very early on in the pandemic, we as Bio, proposed "Can you-" And I think this is, in essence, [01:08:00] what Active did, "Can you put things in categories and then look across those companies and say, 'Let's take five or six of these and six or seven of these and seven or eight of these.'" Knowing that the patient pool is finite and also the ability of those taking care of those patients is finite to do clinical trial versus take care of patients. Was there a way that we could, using a structure like Active in particular, better sequence more [01:08:30] products in the same bucket in, let's say treatment of ARDS, for example, versus treatment of the overstimulated immune system or what were the different things we were trying to work on?

Smaller companies would have been happy to be part of the protocol itself, as opposed to doing their own small trials that weren't very effective, but they couldn't quite figure out how to get in. And I think that as they learned [01:09:00] how to get in, as we started to have active forum, to some degree, I think it was more about understanding, as we were learning more about the disease, what were the things that needed to pivot on if they were going to be considered. And that's why a lot of times in these conversations, in the working groups, I focused a lot on the communications to industry, because I think companies are happy to shift to where the new need is as we learn the natural history, but they weren't always sure if they were behind or in front of the data.

And I [01:09:30] think Active is something we have championed as something that needs to stay for the precise reason that instead of building it every time we have a new disease, let's have something that everybody knows they plug into, all the government agencies are at that table and small and mid and large companies can come with products that are in different stages of development and there can be a plan for late stage development versus early stage potential breakthrough kinds of technologies that could be helpful in an emergency.

Stacey Adam:

[01:10:00] And Phyllis, I'm going to stay with you just for a minute. I know one of the things within the discussion of the work group that we had sort of identified as a gap, and you've just sort of articulated it was, we had preclinical. We had a prioritization process to help people in the preclinical stage and then

we had phase two and phase three trials. So, we really had kind of that middle gap, but I guess, talk a little bit about how much you think we could have brought some of those smaller companies and if we could have somehow plugged the gap between preclinical and the [01:10:30] later phase trials.

Phyllis Arthur: This is a perfect example, Stacey, I think there were companies that already had their preclinical done and were maybe in phase one. They had a really good story to tell, they could not find a place to go that wasn't early stage money or later stage money. And I think that applying that same fantastic way that operation More Speed worked with companies on the vaccine side to some degree collapse phase one, two, and three [01:11:00] probably could have gotten some of these products over the hump on a relatively well crafted, but not huge placebo controlled phase one study and into the two, three category where they could have really shown that they either mattered or they didn't matter.

And companies got trapped in that extra valley of death of phase one to 2A and I think that that is a place where we need to look across the whole ecosystem and realize that it's kind of a hole for medical countermeasures. There's [01:11:30] not really a place to do that, that clearly owns that space between that zero and two. And I think that's one of the things, if we can strengthen that, I think you'll find a lot of companies will happily come with earliest clinical data in humans, they need that bolster to get them over into the more critical 2ATB category.

Stacey Adam: Definitely. And I just want to expand out on that. That was one of the gaps, obviously, that we talked about in working group, [01:12:00] but for the rest of the panelists. I won't necessarily key in who goes first, but the question that I would have for you is, what would be your top recommendation of the gap that we saw that we could address for the next pandemic? And happy to have anybody jump in and have you guys speak amongst each other to build on that, but would anybody like to start?

Janet Woodcock: Well, I think perhaps a fallacy and I understand why that was the case, but is it vaccines were going to fix everything? [01:12:30] Okay. And we have to be pretty sort of cold about this and realize that that might happen and that would be great in any given pandemic, but it's unlikely, especially for a respiratory virus, right? So, having a better pipeline of therapeutics and a more robust effort on a variety of agents, some of them earlier, [01:13:00] would have been good because if the thought was sort of, "Well, we'll get these and they'll just be the bridge to the vaccine, and then everything's going to be fine." Right?

And here we are a year later than the vaccines were thought to, perhaps, have appeared. And we're still in the midst of this for a variety of reasons, and we will be for some time. So, I think I was uncomfortable, frankly, with, I think the short-term view is [01:13:30] important and good to have for one group of candidates. But had we had more money, a longer-term pipeline and a broader view would have been desirable. Yeah.

Phyllis Arthur: I can't reinforce that enough. I think that strategically, I think that at the strategy level, we forgot that we were always going to be treating patients for COVID, and that there was no reason why we couldn't continue [01:14:00] to have funding for innovation in the therapeutic space, across all the different parts of the disease. And that much of that would help us with other respiratory illnesses as well. That there's a spillover benefit. Now, the economist [inaudible 01:14:14] is coming out, right?

There's a spillover benefit to broad therapeutics R and D. That includes the recovery of people who get sick and go to the hospital as well as earlier stage treatments. And I think we [01:14:30] did think that the vaccines were going to be the end [inaudible 01:14:33] all of that. And I love vaccines. I've been in that space for 30 years, but we have to have both a treatment, a diagnostic and a vaccine strategy that is multi-pronged, and multi-year with the idea that it will contribute to our overall pandemic preparedness [inaudible 01:14:46] large.

Stacey Adam: And Elliot. Maybe I can ask you to step in, in how do we incentivize kind of the broader, I guess, R and D larger pharma area to really kind of work towards this. I know you [01:15:00] have some ideas. I know you guys are even probably working towards this, but would be happy to hear your thoughts.

Elliott Levy: Yeah. Let me just, I mean, if I can say a word in response to the last question where, I think, in retrospect, an enormous gap was in antiviral research and development, which not only did we stop working on coronavirus antivirals, but the entire field of antiviral R and D was allowed to go largely dormant as the HIV [01:15:30] and HCV came to be perceived as soft problems. And that meant that there was a huge influx of experienced medicinal chemists and biologists out of antiviral R and D and into other areas.

And that, unfortunately, I think is a challenge that we're addressing, but it's critically important. And the other huge gap that I'm sure everyone would agree is in the availability of platform trials that [01:16:00] can be kept warm and then repurposed in event of an emerging pandemic. I think we all struggled to stand up platform trials and while we were working at it, that the space was filled with small trials of little scientific value.

In terms of incentives, I think there is a, I would say first of all, that there isn't a very good understanding in the industry of the potential [01:16:30] value of investment in pandemic preparedness. And I think there's a substantial amount of academic work that needs to be done to build the investment thesis for the firms. I think it's there, but right now, it's in a sort of a pre-cognitive state where it hasn't been expressed in terms of formal research that can be vetted.

And I think that research would help us to understand whether there are additional [01:17:00] market shaping or market enhancing mechanisms that need to be put in place in order to promote investment, including advanced purchase agreements and stockpiling. And then, finally, I think that there needs to be an honest discussion amongst all stakeholders about pricing globally,

which I think for innovative firms who have to be profit-driven is a major [01:17:30] source of concern. So, I'll stop there.

Stacey Adam: Thanks Elliot. Sarah, any thoughts on-

Sarah Read: Yes. Well, I just wanted to follow up on, I think we're hitting on recommendation number two, which is about ensuring that the clinical trial ecosystem will be capable of producing a clinically actionable evidence. And Janet had spoken about this previously, but that there's, early on in the pandemic, was a desire to [01:18:00] immediately jump into investigating agents even as they were in small, poorly designed trials.

So, I think we have an opportunity, now, to create that blueprint that we didn't have before in the form of, I don't know if it's preparedness so much as a response plan, that this will be our response in the setting of the next public health emergency, so that all companies and investigators are aware that [01:18:30] there will be a response, take some time to set it up. So, ideally people can be part of that unified response as opposed to setting up all of these myriad of competing trials.

So, I think that all of these lessons learned, if they can be communicated much more broadly than just with the group of USG and company representatives that have already been communicating [inaudible 01:18:58] within ourselves, [01:19:00] so that people are aware at academic institutions, at smaller companies, et cetera, that there will be a unified response for the next public health emergency. I think that'll go a long way to cutting down on the competing trials.

Phyllis Arthur: I think the other recommendation I really think is important is recommendation one. I think one of the hard things was we were all learning the disease all at the same time, but not all at the same time. [01:19:30] So, if you had good relationships with a certain thing behind a paywall, you might get more natural history data sooner than if you didn't. Where everyone was trying to do good solid R and D and understand how their technology might or might not apply.

One of the things everyone was scrambling for was an understanding of what was happening with patients on the ground in real time. And so, I think recommendation one is also extraordinarily important if you think of the entire R and D ecosystem [01:20:00] as including industry, hospital, clinicians, et cetera. Having some systematic way to share information on what we were seeing with the disease that is not the New York times, that is more scientific than that, I think would be extraordinarily important in having companies come with their story more online for what we're seeing, and also facilitate, I think, a good discussion of where certain technologies or mechanisms of action might actually be the [01:20:30] most helpful or not the most helpful.

But especially when we're all learning a disease for the first time, the rapidity of sharing information with the scientific community, not the whole public, but in a scientific way is one of the recommendations, I think, could really help with much clearer response to next time. Sorry, Janet.

Janet Woodcock: Yeah. Well, I agree with that. And I also agree with the recommendation about the research findings from clinical, which [01:21:00] were sometimes lagging. We had press releases and so forth. And I think some of that has been improved with pre-print. But I really think that all the recommendations are important. What I wanted to talk about those, Stacey, was I do think that we need a clinical trial network out in the community.

And the reason I believe that is that I believe we need to empower community [01:21:30] researchers or community caregivers to do clinical research and people who are in communities that aren't usually having access to research, right? Or don't have the quality of care, in some ways, because I believe access to research say, for COVID, that probably improved the quality of the care that people were getting. And so, [01:22:00] it's not just about, what we have focused on over the years is inclusion of people in clinical trials who are diverse, but I think we need diverse communities engaged and diverse investigators in rural and underserved communities and so forth.

And I believe we need to do that in between having a pandemic because you can't stand something like that up in an emergency. It requires training and requires long-term commitment [01:22:30] and requires preservation of time for people to do these types of things and participate. But I don't think we'll really have health equity in this country whatsoever if we continue to have the clinical research enterprise be a separate enterprise, it's mainly carried out in specialized centers.

Stacey Adam: Yeah. I think the groups would wholeheartedly agree with you. I think the infrastructure group is going to hit on that, I think, a bit more in the next [01:23:00] panel. But yeah, absolutely heard and understood. I want to open up, we've been getting questions in the chat and so I want to make sure we at least get to a few of the audience questions, that we're not neglecting our folks out there.

Mike, I know you've been watching this. Do you have a few queued up that you'd want to bring forward?

Michael Santos: Yeah. Absolutely. So, thanks everyone for the questions you've submitted. If people continue to submit them, we'll do our best to get to as many as we can. [01:23:30] So, maybe to start off with, one of the questions was, as it's become clear how difficult it is to identify effective therapeutics, how do you think about coming back to evaluating some of the candidates that weren't prioritized initially?

And there's been some discussion already about the persistent challenge and some of the gaps, but I guess, I thought I would throw it open. I don't [01:24:00] know. Sarah, if you wanted to talk about, from the Active perspective, how over time, what you were looking at evolved? And hear from others their perspectives on that.

Sarah Read:

Yeah. So, I think, importantly, when we do our waves of prioritization, especially in the very beginning, we more often than not, wouldn't discard any of the potential agents, but set them aside for the future waves. Like I said, when we first started, we really wanted agents that were ready to go into a phase three trials. So, either already approved [01:24:30] for another indication or very well along in clinical development for some other indication.

But we didn't sort of throw things away. We put them aside so that we can look at them in the future, perhaps when there is more either preclinical data or even clinical data available for those agents. And I think it was mentioned within the question, as we learn more about the disease pathogenesis and became more aware of [01:25:00] which, for example, inflammatory or immune activation pathways are more or most relevant to the disease. We can go back and look at those agents that were targeting specific pathways.

So, we did go back often to look at agents that had previously been submitted. I also didn't mention previously, but very helpful to our process was the development of an agent submission portal that allowed investigators, [01:25:30] companies, anyone to make a submission of an agent that they wanted to be considered by the Active group. And it was organized in such a way that all of the data that we were looking for in order to make a full assessment were requested and hopefully provided by the submitter.

And when we went through our reviews, we would send a message back to the submitter. If we didn't prioritize our agent as to why and what additional information they [01:26:00] might be able to provide either immediately or as it produced it, that would help us to reevaluate their agent. And so, there was a lot of ongoing dialogue with those submitters. Most of whom were from companies so that we could go back and reevaluate agents as more data became available or as we learn more about the disease process.

Michael Santos:

Great. Thanks Sarah. Okay. So, we'll maybe keep going through the [01:26:30] questions. So, one of the questions, a couple of people ask questions essentially about how prioritizing host directed therapeutics versus direct acting antivirals or, in one case, host acting antivirals. How that prioritization was considered and how the current experience with emerging variants of concern might inform that going forward.

Janet, I know in your opening comments, [01:27:00] you mentioned the initial warp speed focus on any virals and maybe you'd like to begin, but certainly others to jump in as well.

Janet Woodcock: Well, again, it was the matter of what data are available, both preclinical and clinical. Is the product available first for clinical evaluation? And then, for warp speed, we were really looking at, could it be scaled? The manufacturing be scaled? So it could be available [01:27:30] within a certain amount of months.

Now, there are some things like interferon and so forth that are currently being studied in these trial. So, I don't think anything was left off the table. It was really a matter of prioritization according to the criteria. So, it wasn't like we said, "Oh. We are not going to look at post directed antivirals." It was like, "[01:28:00] How do we rank these based on the criteria?" Sarah would probably have more info about that.

Sarah Read: Yeah. I would agree with that. So, we did categorize agents initially as immunomodulatory agents, antivirals, and in the antiviral category, we included host directed antivirals. What we called supportive therapy, which was the anti-coagulants and anti-platelets and so on. And also then, we just categorized broadly neutralizing antibodies on their own because we had a different [01:28:30] set of criteria for them, but nothing was off the table.

And we also, as I mentioned, had different master protocols that would be most suitable for each of the different intervention types based on the patient population, as well as the endpoints that were designed in those master protocols. So, we had a place for everything. At a certain point, became a matter of where did we continue to have the capacity to study more agents, but initially everything was on the table. And as [01:29:00] things rose to a level of interest based on our criteria, we did include some of each of those categories in our master protocols.

Phyllis Arthur: The question, Michael, is, was there enough financial and human resources to maybe broaden the aperture for more things to be tested while not sacrificing the clinical trial size that's so important to getting actual real results? And I feel like there's a space between [01:29:30] where more resources, more consistently in this space would have allowed for both the very immediate execution of the strategy that Janet talked about, that's driven by operation More Speed and the broader ability to continue to cycle new mechanisms of action into the categories by Active.

And I feel like in that sense, the mismatch is the funding and the human activity that absolutely did the most we could do with what we had, but had we put [01:30:00] more money in the space, some technologies would now be over the hump that could actually be very useful to us, maybe even now, or in the near term.

I mean, I think it's really surprising to most people that we still don't have a small molecule anti viral, right? When we know that for flu, [inaudible 01:30:16] are great. We also know that we're all trying to solve an access issue. And there are probably some solutions sitting out there. There are probably some solutions for the later stage disease sitting out there, but [01:30:30] there's

maybe not enough bandwidth to fund the work for those, even though there are patients that probably could benefit from those in a clinical trial.

Janet Woodcock: Yeah. Also, If I may just interrupt here a little bit [crosstalk 01:30:44], small molecule antivirals are notoriously difficult to speed along because they have all these big surprises.

Phyllis Arthur: I think actually the American people respect that you said that, because I think the focus [01:31:00] of all of the R and D across the scientific community has been safety trumps advocacy, right? I mean, we really want to make sure, because we're giving it to hundreds of millions of Americans, I think the scientific community has tried to really put forward the idea that we're going to, if it takes more time, but we know it's safer, that's the right answer. And I think the American people appreciate that from the entire ecosystem. That's what we should be doing.

Michael Santos: [01:31:30] Thanks everyone. So, Phyllis, maybe I'll stay with you for the next question, which is that from what's been discussed here, it sounded to this audience member, like a lot of the search for possible drugs was manual or, at best, database searches. And so, the question is, what was the role of chemical informatics in searching and matching with target informatics? And I imagine in Bios constituency, you have a number of companies that are [01:32:00] looking at machine intelligence approaches to accelerating discovery and development. So, maybe you could give for your perspectives on that.

Phyllis Arthur: Yeah. We did indeed have a lot of companies that were aggressively and actively using AI and other things to look at what was on the shelf and really understand its potential for activity against COVID, whether it was SARS-CoV-2 or where the things could be pan Corona. I think that's very much [01:32:30] an active part of this. I think the question they had was then, "What do I do with that?"

But a lot of companies, as I said, some of the smaller companies, they were just trying to find a place to test what they had on the shelf, which was obviously less of a deep bench, but potentially on a mechanism of action. I spent the beginning of the pandemic helping people find a BSL3 lab to test their mechanism against COVID. And I think, as we got over that, people did try to use [01:33:00] informatics to really help them understand the potential so that when they went into the system, they had more robust data.

Elliott Levy: I can just add that in addition to the sort of informatics that you're discussing, that there's a vast potential to use AI and machine learning to scrutinize the medical and scientific literature, which is really under exploited. [inaudible 01:33:25], I think came to surface is an attractive JAK inhibitor for [01:33:30] study based on work with machine learning that teased out a potential secondary antiviral mechanism of action.

I think it's just an example of potential. Those who sat on the agent prioritization subcommittee for Active can all attest to how difficult it is to sift through the medical literature using manual means. And I think that we're at a point in history where the wide availability of the machine learning could vastly accelerate, [01:34:00] not only the pace, but the quality of discoveries from the medical literature.

Michael Santos: Great. Thank you, Phyllis and Elliot. And Elliot, maybe we'll start with you on this next question, and then also open it up. So, there's a question about given all the candidate therapeutics to evaluate, how did you think about head-to-head clinical evaluation? So, maybe some reflections on some of the benefits versus challenges there. Sarah, I know you mentioned previously [01:34:30] the decision within Active for the master protocols to compare explicitly to control rather than the head-to-head. So, yeah. I guess Elliot, Sarah [crosstalk 00:28:38].

Elliott Levy: I mean, I want to leave time for Sarah to respond as well, but I think at the start, until you had a proven effective therapy, you had to have a placebo comparator, and there really is no alternative. And I think once you have an established active agent, then you can begin to use it as a reference in future [01:35:00] trials, which is actually how things evolve. And Sarah, I see you nodding your head.

Sarah Read: Yeah. As I mentioned, we did make that strategic decision, initially, that we weren't looking for the best because we had none. So, we wanted effective therapies, period. But now that monoclonal antibodies are the standard of care, we've had to switch our design to have that as an active comparator. The design is switched in a non-inferiority study for the outpatient [01:35:30] trials, anyway.

It was a slightly different calculation for inpatient, as very early on in our development of master protocols around death [inaudible 01:35:41] became received in the EUA and later, not shortly thereafter, approved. So, that had to be our standard of care on top of which we evaluated additional agents. And I think it will continue to shift as dexamethasone and other [inaudible 01:36:00], [01:36:00] et cetera, have become available, in each case we have to look at each design and in a case by case to ask the question, "Are we looking at a comparison? Are we looking at an on top of?" Et cetera.

And in addition to that, I think that some of these agents, particularly, as we mentioned, for the monoclonal antibodies, the accessibility is still an issue, [inaudible 01:36:22] is an issue. I think we still need to consider agents that are just simply easier [01:36:30] to deliver an oral antiviral agent. For example, for that in the outpatient setting, I think, it still offer a great advantage. And therefore, I wouldn't be looking, necessarily, for something better than the standard of care, but I think that the non [inaudible 01:36:44] design would still be relevant.

Stacey Adam: And just to build on this, and Janet, I'm going to put you a little bit on the spot on this one. Obviously, we chose placebo controlled in the descriptions of what Sarah put forward. [01:37:00] I know, at least in the beginning, and even still some now, we have taken a lot of feedback, let's call it, that maybe we should have chosen pragmatic designs and head-to-head as they did in the UK in recovery and things of that nature.

Now, those were mostly repurposed drugs, and we were testing some novel agents, but what would it take, I guess, to allow something like a pragmatic to become regulatory acceptable? Because that was part of the reason that we chose to kind of keep the designs that we did. We really wanted these [01:37:30] to be rugged and tent. So, is there a way that we can move fast with pragmatics and yet still get the data that the regulatory bodies would need?

Janet Woodcock: Well, I think that's going to require more conversation. To me, it depends on the end-point. When you're talking about an end-point that is clinical judgment and a bunch of stages and everything that an open label trial is, it can be problematic, right? [01:38:00] If you're talking about mortality, it's different. If you're talking about the hospital discharge, that's a matter of judgment and so forth.

And so, it raises all these questions. If you have a home-run drug, like dexamethasone, it really doesn't matter. I mean, you have such a large treatment effect, right? But here, often, we haven't been looking. Now, in the outpatient setting with the monoclonals, we had a very large treatment effect [01:38:30] if you took high risk people and unuse those. But that would be risky because you don't know what kind of effect you're going to have and the smaller your treatment effect, the more important, I think, it is to have blinded control because there's so many factors that can lead to misinterpreting the results, otherwise. So, I really believe in pragmatic trials. I think they're having a very important role and I [01:39:00] don't think they're done often enough, but I think we-

PART 3 OF 4 ENDS [01:39:04]

Janet Woodcock: ... Don't think they're done often enough, but I think we do have to think about this setting and the end points in particular and how subjective all this might be. So, it really does continue to require conversation. I think it would be really good if we could do more pragmatic trials in... And this is outside of this discussion, but if we had a trial network and did a lot of trials on [01:39:30] what works best and what should treatment policy be in a given disease and so forth and so on, those are basically comparing one regimen or one treatment policy to another. Those are the kind of trials that you really could get used to having no placebo group per se.

Michael Santos: Great. Thanks, Janet. And actually, maybe we'll stay with you to start on this next question. So, during a public health emergency, [01:40:00] what should be incorporated into trials for other indications, for example, oncology trials? So, I

guess maybe there are a couple of questions there about what can be learned from trials for other indications. Also, maybe how an epidemic pathogen compromises other research objectives, but would be interested to hear yours and, of course, anybody else's perspectives on that.

Janet Woodcock: Well, lot of things had to be modified during COVID, so that trials, especially for life-threatening diseases, you can't [01:40:30] just stop them, so they could go on. We discovered that telehealth is actually... Patient visits actually work very well in many settings. We learned that we can use different monitoring... Remote electronic devices to find out certain things. We learned that we could do informed consent, we learned this from COVID, on the patient's cell phone and so forth. So, I think a lot [01:41:00] of those things will carry through to general practice, just like much more telework is probably going to happen around the world as a result of this. As far as what could those trials do for COVID, I have less insight into that. Be interested in the other panelists.

Michael Santos: Does anyone want to add anything [01:41:30] to that?

Elliott Levy: Well, I think we could adopt for, particularly for outpatient trials and COVID-19 and other pandemic agents, many of the same procedures that were used in our outpatient clinical trials in other disease areas, including remote evaluations, remote informed consent, in-house visits [01:42:00] when nursing care is required, use of local investigative facilities, local labs, local radiology, and the direct to patient shipment of investigational product. All the things that we did during the pandemic for all our other therapeutic areas. They're all, I think, potentially relevant for antiviral outpatient trials as well.

Janet Woodcock: Yeah, well, ACTIV-6 is using a lot of those techniques, it's partly fully removed. [01:42:30] Of course, these are repurposed drugs that have a long safety track record that they're using or well understood record, they're oral agent, so you don't have to fuss around about a lot of things. So, they're able to enroll those patients remotely and assess them remotely. So, yeah, that is happening.

Phyllis Arthur: [crosstalk 01:42:53] Oh, sorry. Go ahead, sorry. Go ahead.

Sarah Read: I was just going to point out that I think early on the clinical trial capacity working group [01:43:00] put together, I think they called them playbooks, which were best practices for a lot of these activities that would turn remote that had once been in person and they might touch on that and another panel. But I think that since then, each of the protocol teams have also developed really useful tools that we should consider somehow also making available, not just for future outpatient antiviral [01:43:30] trials, but then for other trials that might be occurring in the setting of a pandemic or not. It just might increase efficiency and so, could become now the new way of implementing clinical trials.

Phyllis Arthur: I think that's very much what I was going to say, is Janet talked about we need to get the trials more closer to the communities so that we can really guarantee the diversity of investigators. Referring physicians can investigate locally and [01:44:00] people can go to trials that are near them in a place they recognize. And some of these things that we learned doing these trials that make it easier to be in a trial, actually, I think, are part and parcel of that diversity mechanism, right? So, if I'm a busy Medicaid physician and I know that my clinical trial patients can do a call with the nurse running the study and not come in my office, that might help me feel comfortable being an investigator. If I work for a living in a job where I can't take off an hour and a half, [01:44:30] but I can pop on my phone for my check-in with the clinical nurse on my lunch break, these are the things that might really help with the diversity mechanisms, just thinking about the way people have to live their lives right now.

Michael Santos: Great. Well, given the time and the content, this is a perfect opportunity for us to wrap up this panel and look forward to transitioning into the subsequent panels, which are also going to talk more about infrastructure and resourcing for clinical trials and execution of clinical trials. So, on behalf of [01:45:00] Stacy and me, I want to thank Janet, Phyllis, Sarah, Elliot, again, for your contributions throughout the pandemic and on today's panel and we're all looking forward to enjoying the rest of this meeting. So, I think, with that, we'll turn it back over to you, Kevin or Susan, whoever is up next. Thanks.

Susan C. Winckler: Great. Thanks so much, Michael, and thanks to everyone of those panelists. I feel like we've just been given the first edition of our master class in thinking through this lessons [01:45:30] learned exercise and really appreciate the investment of each of our speakers and our panel moderators in helping us consider what we might change and a good path forward as it relates to research scoping and prioritization. And as you said, Michael, it's time then for everyone just take a deep breath, because we're going to head into panel two and I expect the discussion is going to be just as robust and [01:46:00] educational.

For panel two, we are going to look at infrastructure and resourcing and our moderators here are each from Faster Cures, Esther Krofah, who serves as the Executive Director at Faster Cures and the Center for Public Health with the Milken Institute. And her colleague, Kristen Schneeman will be helping us dig into the recommendations that are relevant in this area [01:46:30] as well as then react to the really excellent questions that we're getting through the Q&A and the chat. So, if I may, I will ask... Kristen, I see you're coming up on camera and Esther, you're coming up. I'm going to step out of the way and allow you and your panel to take over the platform. Thank you.

Panel 2: Infrastructure & Resourcing

Moderated by

Esther Krofah

FasterCures and Center for Public Health, Milken Institute

Kristin Schneeman

Director, FasterCures

Panelists

Barbara Bierer, MD

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

Michael Kurilla, MD, PhD

National Center for Advancing Translational Sciences, National Institutes of Health

James Mayne, PhD

Pharmaceutical Research & Manufacturers of America

Doug Peddicord, PhD

Association of Clinical Research Organizations and Washington Health Strategies Group

Kristin Schneeman: Great. Thank you so much, Susan. Really appreciate it, and glad to follow on that [01:47:00] excellent first session. It did very much touch on some of the issues we'll touch on in this session as well. So, let's get going. So, my name is Kristen Schneeman. I'm a director at Faster Cures, which is a center of the Milken Institute. We were responsible as part of this overall effort for leading the group focused on the infrastructure and resourcing needed for effective clinical evaluation of therapeutics, specifically within the context of the current public health emergency and future ones.

But we [01:47:30] believe these lessons learned very much apply to our ability to effectively evaluate therapeutics outside the context of a public health emergency as well, which is why we were eager to be involved in this effort. I'm here just to give a high level overview of our working group's recommendations, and then I'm going to turn it over to Esther Krofah, Faster Cures Executive Director, to lead the discussion with our distinguished panelists, several of whom were active participants in our working group. And if you want to go ahead and bring up the slide with the recommendations [01:48:00] on it. So, our first recommendation, we had five, centers on the importance of identifying and leveraging existing clinical trial infrastructure and public private partnerships and deploying them against high priority unmet needs between public health emergencies, and you've already heard some discussion of that.

Some of these networks and partnerships like ACTIV, like CoVPN, were built on the foundation of existing infrastructure initiatives and proved [01:48:30] quite effective during COVID. There were gaps, however, in maybe fully engaging, for instance, the VA's extensive network, maybe federally qualified health centers in some of the COVID research. So, there were certainly gaps that we should look to address. Developing a plan for setting and funding, research challenges, so to speak, to keep this research based warm, heard that term a couple of times already, would help ensure that it's in place when another public health emergency occurs. The second recommendation addresses [01:49:00] the need

to build, engage, and support more community-based institutions and networks to improve the representativeness of clinical trials and our ability to deploy more pragmatic trials across the board. Those of you who tuned into the previous session heard Dr. Woodcock and others emphasize the importance of this recommendation.

We certainly saw, during the pandemic, the difficulty of reaching patients everywhere across the country, in places beyond the reach of academic medical centers and especially those in historically underserved communities who were hardest hit. [01:49:30] This recommendation is aimed at what it would take to build greater capacity and partnerships for conducting clinical research in more places, as well as promoting more pragmatic designs to enable easier engagement by more sites. And you're going to hear many of these themes in the clinical trial execution panel after this one, as there was a lot of synergy between our group and that one on recommendations like this. The third recommendation is focused on removing post-pandemic barriers to expanded adoption of decentralized and hybrid [01:50:00] trials and remote monitoring tools. Again, something we've just heard at the end of the last session. We've all certainly seen the rapid transition to greater use of decentralized and remote approaches to research studies and monitoring as well as care.

I think we've all personally probably benefited from that over the last year and a half. What might had been considered risky by sponsors and providers in the past, all of a sudden became necessary risk mitigation. But many of the flexibilities that were put in place for the public health emergency will not naturally persist with its end, [01:50:30] so purposeful action has to be taken to ensure their continued use, improvement and growth. The fourth recommendation addresses challenges with patient enrollment, particularly the need during a public health emergency, to prioritize enrollment in well designed trials. Again, something we heard discussed earlier and I like Dr. Woodcock's phrase earlier that it felt like we were starving in the midst of plenty sometimes. And this recommendation, as we unrolled it, sort of speaks to more effective communication strategies, embedding clinical research [01:51:00] tools as part of routine clinical care and establishing guidelines for co-enrollment, which was challenging in this context.

And the fifth and final recommendation returns to the need to increase participation in from underrepresented communities and create action plans for improvement. The previous recommendation, number two, was focused more on the sites, networks, partnerships, while this one was a more squarely at reaching research participants. There are many examples organizations that have been successful at engaging diverse communities and research. [01:51:30] We saw some successes during the pandemic within [inaudible 01:51:33] initiative, which we heard about from Dr. Collins and some of the vaccine trials, recruiting significant numbers of racial and ethnic minority participants. So, there are playbooks and success stories but also, many obstacles and challenges in terms of resources, policies, and coordination that need to be addressed. And this is certainly an area of great interest and focus for Faster Cures going

forward, as we know it is for many of the rest of you as well. And I'm going to stop there and hand it over to Esther and our speakers.

Esther Krofah: [01:52:00] Well, thank you so much, Kristen, and welcome to all of our panelists. And it's been a great conversation so far throughout the day, and no doubt we'll keep up that energy with this panel as well. Many of you, of course, participated in our working group process and so, you're quite familiar with those recommendations that Kristen just outlined. Why don't I introduce the panel and then we'll get going in terms of our conversation? First, Dr. Barbara Bierer [01:52:30] professor of medicine at Harvard Medical School and faculty director and director of the multi regional clinical trials center, MRCT, as many of us are familiar with her work. Dr. Doug Peddicord, who's executive director of the association of clinical research organizations, ACRO, that was referenced by Janet in her comments and president of the Washington Health Strategies Group, so welcome.

Third, Dr. [inaudible 01:52:58], who serves as the vice president [01:53:00] and senior advocacy lead for PhRMA, welcome to you. And then finally, Dr. Michael Kurilla who is the director of the division of clinical innovation at the national center for advancing transnational science, so NCAs, part of the NIH. So, welcome to all of you. There's a lot for us to talk about. A lot of the themes really emerged in the earlier conversations today, both in the keynotes, by Dr. Woodcock and Dr. Collins as well. But Barbara, I'd like to start with you just [01:53:30] to offer your thoughts. We've gone down this memory lane of the last 18 months or so of the pandemic and the response to the pandemic, and you've been also quite well situated in the midst of the response efforts from your vantage points in capturing these lessons learned. So, I thought you could offer your reflections over the last 18 months, particularly those early months around the challenges with infrastructure and resources, which is our topic for our panel today. What [01:54:00] did you see and what are some of your observations looking back?

Barbara Bierer: So, thank you so much and thank you for inviting me and thank you to [inaudible 01:54:09] for arranging this really wonder full day, and the first session was just fantastic. So, if we drop back to Boston in March of 2020, where we had just had a super spreader event, let me remind you all that we had deployed every hospital [01:54:30] bed based, basically, and every ICU bed to COVID-19. We had no therapies, we had sort of repurposed all of the resources and many of the individuals that were there to care for COVID-19.

We were all really beleaguered with the fact that we were trying to treat patients without any tools, information, even natural history. [01:55:00] And we stopped all of clinical research other than that related to COVID-19, which for issues like oncology was problematic at best. And then went into a period where we, as every institution, basically on its own in the early days, stood up individual trials, which were then, because there were so [01:55:30] many people who wanted to study it, had to be prioritized based on resource constraints. And none of those trials really had the statistical power to be

contributing to generalizable knowledge. Now, exactly why that was, we will get into.

But what we learned over several months is we needed and still need leadership and governance, not [01:56:00] just at the institutional level, but at the regional level, the state level and then, the federal level, and then collaboration externally. And we were thankful, I think, for the many wonderful efforts at partnership that came, if anything, for us, felt late, but better late than never, and I think that was really important. This issue of how to triage and deal in resource limited [01:56:30] settings, which we found ourselves at the Harvard Hospital's resource limited, sharing PPE kind of thing, it was part of the pandemic experience and one where we found that the more organized we were, the better it was.

What became clear, however, is that we were seeing a host of patients that were under served and underrepresented in medicine, [01:57:00] in our hospitals, and that we did not have either the network, the infrastructure or the collaborative platforms to reach out to the communities in effective ways, even locally. Now that has, I think, changed and I think if there's any silver lining here, it's that we are ready and committed as a society to address of these problems [01:57:30] and I think this is part of why we're here together. I also think infrastructure used to be a dirty word, essentially, and nobody would... But it's been so critical. I mean, as Mike knows, we've been working on a system of IRB review to allow reliant review, and just having that in place allowed the really remarkable collaboration across [01:58:00] institutions, such that the fastest determination of reliance was 16 minutes across institutions.

Where there was no need anymore, because we already had it, to figure out how to do it. We need to do that in every aspect of what we do, and then on a sort of more global scale, in many ways, establish the communication pathway, so that even [01:58:30] if they're setting up individual trials, the endpoints are comparable, the data definitions are comparable. We can then inter operate the individual patient level data with appropriate confidentiality and privacy provisions. And then make sure that we communicate to the communities and those affected with health literate, language concordant [01:59:00] materials. We learned a lot about trust in the last 18 months, and I think we have a long way to go to rebuild that or to build it anew in communities that we have served poorly.

So, I do think this idea that we need to do a much better job of reaching out to the communities, and not just in a paternalistic way, [01:59:30] but believing and acting in a way that is authentic, that the community should drive much of what we do. It's not from the academic centers to the communities, but it's figuring out how that really is a network that is a partnership. We've done a lot of work at the MRTC Center on diversity inclusion and equity, have lots of practical recommendations, but there is nothing compared [02:00:00] to seeing the kind of partnership and respect that we've seen over the last number of

months come to bear. So, I'm going to stop there and then happy to pick up on a number of themes, but I know what others are going to say, so...

Esther Krofah: Well, thank you for that, Barbara. Those were great opening comments and there are a number of places for us to go further in conversations there. Doug, we're talking about infrastructure and the CRO networks were being called upon, [02:00:30] either through industry or through the active collaborations and otherwise, to stand up trials rapidly. So, maybe you can share a bit about your experience the last 18 months and what you observed and what some of the challenges were.

Doug Peddicord: Sure. Thanks very much to Esther and thanks so much for of the invitation to be on the panel today. And I must say I have beat the drum for a really long time on the issue of how can [02:01:00] we better set up public private partnerships, such that we can take advantage of existing trial networks, as opposed to always trying to build a new trial network. And I think the pandemic really certainly brought that message into the light. Quick note, just on the large global CROs and the kinds of networks that they [02:01:30] maintain. So, they really have two sorts of trial networks. One is a small set of owned clinical research sites, and those are often phase one units, dedicated research sites that do phase two, three research across a variety of therapeutic areas. That I would characterize as the standing network.

[02:02:00] There is a smallish, but standing network that is really available to do new clinical trials across a variety of areas. There's a different and much, much larger clinical trial network that the large global CROs maintain and they call them variously preferred sites or ready sites. And I think this is the set of clinical trial sites [02:02:30] that have been through qualification, preparation, activation, on one or more clinical trials previously and so, they can be thought of as experienced sites, so they're preferred sites for the CROs. And I would think of that as not so much a standing network, but a ready network. It's a network that can be in some ways put together to be purpose-built for a particular [02:03:00] situation like the pandemic was, and those sites importantly are warm sites. So, people have talked about that phrase a lot. Clinical trial sites need to be kept running in between pandemics.

We really can't have a dedicated pandemic trial network, that simply is isn't going to work. I do think the way that those preferred [02:03:30] sites have been developed, I think, is that historically the CROs have committed to, what I would call, the democratization of research. So, in addition to working with academic medical center, the CROs for a very long time have worked with community hospitals, with large and small practices, with dedicated research sites and I think that democratization is... [02:04:00] The previous panel, I think, mentioned the issue of the need to embed research into care-based settings, that people talk about clinical research as a care option. And I think the flip side of that is, it's important to put research into care-based settings. So, this is the sort of approach that I think HRSA and a AHRQ often take, [02:04:30] which is going into community sites and placing research into those kinds of sites.

So, all of that is background to then the sum of what worked well and what worked less well. I think the partnership with a number of the active studies was important. I think what it illustrated was, not only how difficult it can be to set up new trial networks, [02:05:00] but also then the huge number of pure project management functions that many of the large CROs bring to the table. So, now I'm talking about things like managing a central IRB and the local ethics committee submissions, doing contracting, management of site documentation, 1572s and the like, developing country and site informed consent forms, site [02:05:30] monitoring, et cetera. I think those pure project management functions were very much part of bringing those to bear. I think allowed for, certainly, some of the active studies to proceed more quickly.

The last thing I'll mention just in opening comments is one of the things that the pandemic clearly brought for us [02:06:00] was the rapid shift toward remote and decentralized activities. So, one of the things we do is a survey every year of ongoing trials, roughly 6,000 undertaken by large CROs that are in our membership. And in February of 2020 ongoing clinical trials, 82% were using onsite monitoring [02:06:30] in February, 2020. By April of 2020, and the first wave of the pandemic, there had been now 93% of trials were using off site monitoring. If you want to know how trials kept running the extent to which they did, it certainly was the very rapid transition to offsite and remote activities, and that I think was really allowed by two things. [02:07:00] One, was by the preparation that had gone into establishing decentralization of various kinds of trial functions, and the other was certainly regulatory flexibility from the FDA and other regulars.

So, I think that will be something that we're going to hope we'll continue on into the future. I will say, we're doing a study, at this point, of DCTs [02:07:30] and always comes down to... Definitions are important, what counts as decentralized? What counts as hybrid? But we're looking at just certain functions. So, you look at everything from eConsent and e-signature to direct to and from patient shipments, to home health visits, to telemedicines, which are medicine, which already been mentioned, to [inaudible 02:07:54] and ePRO and connected devices and the like. I think it will be [02:08:00] interesting if one of the learnings that we take from the pandemic certainly is that the move to remote and decentralized or hybrid trials is something that actually is really good for everybody, most especially trial participants. So, let me stop at that point, Esther, and thanks for the opportunity to be here today.

Esther Krofah:

Well, thank you so much, Doug. And Barbara made the point, which is going to be a theme throughout, [02:08:30] infrastructure is not the sexy topic until it becomes the rate limiting factor in speed, and you certainly touched on some of those items as well. Jim, I want to call on you just to reflect as well, your experience over the last 18 months, working with your companies and trying to one, keep trials going on, and Doug talked about some of that, but also what the infrastructure needs were to work quite quickly across issues [02:09:00] like contracting indemnity and IRB, all of those nuts and bolts of how do you establish trials quickly. Maybe you can offer your reflections.

James Mayne:

Well, thank you very much, Esther. And I want to thank the organizers for the opportunity to join this important discussion. Certainly, the experiences of the last 18 months have been extraordinary for all of us and that includes those of us in the biomedical pharmaceutical industry. [02:09:30] I would like to start in that vein, with acknowledgement of all of the extraordinary efforts that have been made by different parts, different stakeholders in the biomedical ecosystem, to move and move quickly with the COVID vaccines and therapeutics. Including, not limited to by any sense, but including the critical dialogue and feedback between industry sponsors and regulators, so that we had clear expectations [02:10:00] for what evidence was appropriate and what designs were most appropriate for moving forward with clinical research.

That was the enabler of all the rest of the work that we're talking about. In the context of infrastructure, I do want to also recognize, as Doug did, that it's important to note, and it's an ongoing challenge, the impact of the pandemic on the continued progress of innovative experimental [02:10:30] medicines that are under development, other than those that are being developed as COVID counter measures and also, on the production and supply of existing medical products. So, both of those things needed to continue, they needed to continue under very difficult circumstances while juggling those three balls with two hands while another ball was being juggled, trying to make these breakthrough therapies to [02:11:00] address the COVID pandemic. Working with shared purpose and urgency, highly interactive discussions were rapidly advanced and identified, innovative solutions for these challenges...

PART 4 OF 4 ENDS [02:11:18]

James Mayne:

For these challenges such as those discussions that help address the challenge of conducting regulatory inspections during a pandemic, a very critical element of infrastructure and maintaining the activity in the infrastructure. Similarly expanded use of innovative clinical research approaches, others have touched on this such as decentralized trial and some of the other e- fill in your favorite tool, technologies [02:11:48] that have been deployed, and expanded in their use over the course of the past year. These things collectively have allowed both those development programs to continue, and importantly the flow of critical medicines to continue. So, what were some of the infrastructure based critical success factors that we've seen and that we, we learned about during the pandemic?

First, companies had the existing [02:12:08] platform, capabilities and deep experience and expertise to translate this basic science that came out of the learning process into testable exploratory medicines. So, that's a part of the infrastructure that shouldn't go overlooked. That's the basic ability to translate information knowledge into real testable molecules. Second, companies were able to deploy and redeploy key resources such as clinical resources, which have been discussed, but [02:12:38] I want to highlight manufacturing resources as well, because manufacturing, as we've all learned, watching the vaccine story, and we focus on therapeutics here, but watching the vaccine story, don't

overlook that [meta 02:12:50] manufacturing, it's critical to advancing research, and it's critical to having products that are available as soon as they're considered suitable and either authorized or approved by regulators. Third, companies collaborated effectively with each other, and at ways, and [02:13:48] at a level that we had never seen before, and with regulators to understand how to best study and advance these new treatments. We heard reference earlier to the COVID R&D Alliance that was certainly central to those efforts, but by no means the only effort in that regard.

So, really new definitions of what the ability to share and partner within and across industry was identified. [02:13:18] And then, finally companies were able to anticipate and front load activities that are typically done in sequence. This was another part of the secret sauce that did allow, and continues to allow, these development programs to advance extremely rapidly. And, that's things such as front-loading the developments of manufacturing process and controls and scale up. These things being done at a time in the development cycle where [02:14:48] under typical situation that they would not. That front-loading, that parallel processing was, I think, an immensely important part of the ability to move rapidly, but also carries with it uncertainty and business risk that I think we can have address through these types of discussions.

So I'd like to close by noting that this pandemic response experience over the last 18 months so far, because we're not entirely [02:15:18] out of these woods yet, demonstrates that biomedical innovation can be done with a thoughtful balance of purpose, caution, and urgency resulting in outcomes that are a benefit to all of us, patients and society all alike. And learning from these experiences there, then it seems reasonable that similar approaches could be applied to other urgent medical needs. And learning from these, we can broaden our application of these tools and these learnings beyond [00:04:00] pandemic preparedness, beyond being ready for the next global pandemic. So I'll stop there, and hope these comments were of interest

Esther Krofah: Yes, absolutely, Jeb. And we'll come back and talk about what does it mean to keep things warm and ready? That's certainly a theme that's come up, and what's the infrastructure that we need in order to sustain networks in between these public health crises? But they're also applicable for other disease conditions as well. Dr. Kurilla, [02:15:48] I want to bring you into the conversation. We've certainly heard a lot today around the role of the NIH networks, whether with SEAL being leveraged for the active trials, maybe you can take us behind the scenes 18 months ago when all of that was being identified and stood up, and you went through this exercise of creating an inventory of NIH assets. What was that like? What did that mean? And, how are you maintaining that?

Michael Kurilla: Yes. So thank you, Esther. Yes, it [02:16:18] was a rather novel experience to say the least. I think when I was tapped to take on the active clinical trial capacity working group, and try to assemble the clinical trial network capacities that we had in the capabilities, I think it became abundantly clear early on that no single

clinical trial network was going to be able to address what we were envisioning was going to be needed. And, I [02:16:48] think the first thing that that required was an inventory. And what became obvious in that working group was that no single entity, either NIH or the pharmaceutical industry, or a lot of other entities that were involved, everyone had something to contribute. And it was really a matter of coming together and trying to put everything on a standard scale, recognizing that networks are generally designed, they're rather bespoke [02:17:18] in terms of how they're constructed. They're usually put together to do something relatively specific.

And so one of the first things we had to do was survey across everything that everyone would make us aware of, to be able to put what everybody's capabilities and capacities and interest, to a certain extent. Recognizing that while we were trying to stand up some rather large trials, there was a lot of other activity going on, both within academic centers, [02:17:48] feeling the need to do something, as well as the pharmaceutical industry, wanting to move as quickly as possible in terms of what they thought might be contributory. And so, that was the first effort and it was quite successful in being able to bring together very large assets under one single database, an inventory of what we had available that was utilized by a wide array of clinical protocols that were eventually [02:18:18] developed.

I think some of the other things that became unique, it was mentioned in the earlier panel, that we put together a series of playbooks, recognizing that things were not going to be able to work as normal or typical under this environment, because, as it's been mentioned by other panel members, the remote requirements and an expectation that every site was going to figure it out on their own was not going to be very tenable over the long term. And so we needed to provide as many resource capabilities and options [02:18:48] to make people aware of, and disperse that as quickly as possible. The other thing, I think, that was unique in terms of, at least in the early days was we also had major, which I don't think anyone really anticipated, major supply chain issues. And so it wasn't a matter of simply having a budget line for PPE or nasal swabs. There were many sites who said, "no, don't give us money for nasal swabs, send us the nasal swabs in order to be able to conduct the study that you want us to [02:19:18] do."

So that was a rather unique aspect that we really hadn't thought about or considered, I think. It's usually has not been, supply chain issues have never really been a major problem before. So that was another unique aspect of being able to adequately resource those trials that were being considered, and to think about what was actually being asked for. Just to comment a few on some of the commentary I've seen in the chat. [02:19:48] We have utilized quite a bit in terms of more community hospitals away from academic medical centers, having been involved in some of the largest convalescent plasma trials. Some of our best recruiting sites were actually more in community hospitals and there they require a much higher level of engagement and working with providing them within many cases, dedicated staff and the resources.

There's also a recognition that sometimes some of the master protocols [02:20:18] that are looking at multiple interventions, the randomization schemes, and the involvement in terms of what has to be done as per that protocol, that just may be beyond the scope of many of these smaller healthcare facilities, and recognizing that, well, there may be a lot of very valuable, scientific medical questions that can be addressed in this trial, getting to the answer as quickly as possible as simply as possible, there a trade off and a balance that has to be recognized and really discussed, [02:20:48] as that protocol is developed. I think in terms of engaging them though, I think it's something to think about to really find things that we can be doing in the interpandemic period in the future to keep that warm base available. I think there are many scientific and medical questions that they would be a very perfect place to be able to consider using. And I think it would be very valuable in an overall public health setting to keep that going. That will require an enormous [02:21:18] amount of resources going forward.

One other issue though, that I would address is there was one comment about using historical controls. I think it's important to recognize that for many chronic diseases that may be quite appropriate, but in case of an emerging infectious disease, the natural history does change over time. And so you can't just simply look at what was going on in New York City or Boston in May and April of 2020, and compare that to what we see today. So I [02:21:48] think you have to recognize that as we go forward over time, placebo arms actually have to be refreshed constantly, because the natural history will change as the pandemic itself and the outbreak evolves, but also as the clinical care and the standard of care really changes over time, taking all that into consideration. And I'll stop there. Thank you.

Esther Krofah: Thank you so much. Well, why don't we just continue with you for a moment and then we'll [02:22:18] come back and have everyone else comment. One question, maybe two, for you to think about quickly and comment on quickly. One is, what could these networks do in the interim when we talk about keeping these networks warm, what would that require? And then secondly, what surprised you the most when you went through the clinical trial capacity and the inventory? What did you walk away with to say, "you know what I'm surprised as a country that we don't have [02:22:48] sufficient resources in X, Y, or Z? What were your reactions to those two things?

Michael Kurilla: So I think in terms of your first question, what could we do to keep them in warm based, in other words? I think there's probably a tremendous amount of comparative effectiveness research that could be undertaken, that would be very valuable, that is very hard to resource at the moment. And quite honestly, I don't always think that academic [02:23:18] medical centers are the perfect place to be doing that. I think a lot of strategy trials in terms of different ways to approach diseases, that where there maybe isn't general consensus, that's a very obvious thing to be doing in a wide array, diversity of healthcare setting. You talk about, obviously, diversity of the patients coming in, but I think we also

have to consider the diversity of the healthcare settings in terms of implementation of various [02:23:48] types of medical practices.

And so I think that that's something that should be considered if we actually have the adequate resourcing and funding to be able to undertake that. I think there would be a lot of valuable, it would be very productive to the overall public health of the country and the rest of the world. In terms of what I walked away from, I think what really struck me is there probably isn't a single agreed upon definition of what exactly [02:24:18] a clinical trial network is, exactly what it's for, and what it's supposed to be doing. So, the non uniformity was one thing that struck me.

I think the other aspect that I really learned to appreciate looking across NIH is there's a tremendous dynamic range in terms of funding to individual institutes and centers. And that's not anything that [02:24:48] I or people at NIH have anything to do with, that's the consequence of congressional funding, and that's just the way it is. But recognizing that certain ICs, because of their size, can do things in terms of what they can provide through clinical trial networks that allow them to take on certain types of unmet medical needs and address certain types scientific and medical questions, that other types of ICS [02:25:18] that don't have that resourcing, don't have that scale or that critical mass, can really undertake some of those equivalent types of issues and scientific and medical questions in their specific fields, because they simply don't have that degree of resources to fall back on.

Esther Krofah: Thank you so much. Great points there. Barbara, I know you've developed a wishlist of what you would like to see differently [02:25:48] going forward, what are those items for you in keeping these networks warm? And what are the gaps, particularly in bringing in more of the community based settings? And Mike talked about how they're more resource intensive, so what should we do differently going forward?

Barbara Bierer: So, great, great. And I don't think we have time for the entire list, but let me start with a few and just to annotate Mike's comments for a second. I think we need to be [02:26:18] careful that we begin to disaggregate clinical trials when we just talk about clinical trials, with large, there are comparative effectiveness research where we're doing sort of looking at practical, well, not practical, but comparative approved medication versus the kind of innovator molecules and approaches that Jim was talking about. And those require a different organizational [02:26:48] thinking, which is in part risk based for the participants. So I think we should be careful that we don't try and impose trials that might be more risky than they should be in settings in which they at least initially don't belong or don't belong today. So I think we should start to be pretty careful about how we talk about this.

[02:27:18] The second thing is I think we need to also do a much better job, not only of integrating research into care, but also thinking about the operational issues, the privacy and confidentiality issues, that are embedded in that, which

could then do damage in terms of trust and assumptions. I think we need [02:27:48] to figure out things like how to assess social determinants of health as a routine matter, in a way that is non-stigmatizing or discriminatory, and that is respectful. We don't even have standards for that. And the standards for the NIH SDOH are different than HRSA, that FQHCs have to report.

I think we've underutilized and undersupported our [02:28:18] community health centers, which a different agent, agency or whatever, department supports in terms of their both willingness interest and capacity to begin to get involved in this. And we need to think through many of the policies where we've created an infrastructure at the NIH that is not deployed necessarily [02:28:48] by industry and that that infrastructure similarly not extended to CHCs or FQHCs that are elsewhere. So I do think that there's a real need for an overall look across departments, and departments I mean federally, then we can talk about international for the kinds of things that would make a difference.

And [02:29:18] I'm loathe to talk through what I think the kinds of questions that should be instituted for the community centers in terms of the keep warm questions, because I think we should start with engaging the communities themselves, and seeing what they want to investigate and how we can support them rather than the reverse. And [02:29:48] there's much more to talk about there, but the one thing I will say about digital and DCTs, Decentralized Clinical Trials, we've had a lot of experience now, and I think we do have to be careful that we just don't create another have and have not, the haves that have access to smartphones and digital connectivity, [02:30:18] and those in the community elderly, I know we're supposed to say older people than elderly because I'm one of them, where they need more support, more help, and where the actual technology itself is or can be a barrier.

So I think we have to think through what we provide, and [02:30:48] to create a research infrastructure that is inclusive from its beginning and planning, through its execution and data, and results and return of results. So I can keep going, but.

Esther Krofah: Those are great points and a great list, and a lot of work to be done to achieve all of that. Doug, I wonder if you can comment as well because you raised this topic earlier that there's no such thing as a ready made pandemic [02:31:18] clinical trial network. It has to be doing other things in the meantime. And to the point that Barbara just raised, which is that those questions have to be developed with the community themselves. What's your reaction? What are your thoughts?

Doug Peddicord: Yeah, in terms of the question about resources that Dr. Kurilla raised, which is we need to think about how do you resource community centers [02:31:48] in undertaking research, and I agree with Barbara that that one clearly needs to look at what's that mean, what kind of research, in regard to what the community does or doesn't want to pursue, but I would encourage us to not do the usual either/or, which is either community sites [02:32:18] can be funded

federally, or community sites can be funded by industry sponsored trials. In fact, it seems to me that a big piece of the keep warm possibility comes from having sites that can do a variety of kinds of research.

Academic medical centers clearly pursue [02:32:48] both federally funded and industry sponsored research. And they reap different benefits from those differing kinds of funding sources, but it allows them to have a larger resource base. And so I really would like to make a plea for don't make this and either/or choice. I think that's my big one. I think we need to continue.

[02:33:18] I think one of the things that certainly the vaccine trials benefited from enormously, obviously the therapeutics trial somewhat less so, but was the significant collaboration between FDA and NIH. I think that was a fundamentally important factor in the work that was done. [02:33:48] So I want to continue that, if FDA and NIH can in fact proceed together or at least be collaborative, then I think the option of looking at both industry and foundation and federally funded resources will be important, if we really are going to develop a more community based kind of network, which is I think, soft and ready. I think [02:34:18] it is ready and warm as opposed to a standing network. I think that's more infrastructure that's very difficult to build. And, so I think we need to think about ready networks.

Esther Krofah: And to that point, Jim, I wonder if you can talk about the role, we've talked a lot about decentralized trials, hybrid trials, remote tools, [02:34:48] the use of technology. It was important to keep other trials ongoing while we were pivoting to COVID 19 trials. But as we think about the future and the lessons learned, and certainly those studies are happening right now to understand what worked and what didn't work, even the use of those remote tools, but what is the future as we are thinking about how do we keep these networks going? But how do we also bring in more diverse [02:35:18] participation? Do you think that these offer an opportunity in that? Not an either/or, but of both/and. And what do you think about the role of leveraging new tools that can allow and broaden the kinds of sites or non sites that can participate going forward?

James Mayne: Yeah, thanks for the question. I think the potential is huge. The past is bringing the patient to [02:35:48] the clinical trial site. The future is bringing the clinical trial site to the patient. That's very clear. And I think that's something that will become pervasive across the ecosystem over time. We're clearly not there yet. And as you say, we're still kicking the tires on this and learning what works and what doesn't. And we lack, frankly, a sound and an experienced regulatory infrastructure to do much of this. But we're learning rapidly. And, [02:36:18] I like to paraphrase that working at and learning at the speed of science, I think it applies here as well, is a tremendous amount of this sort of digital and e-technology that is becoming part of the day-to-day life of the clinical trialists and the clinical trial networks, in a way that it wasn't even just a couple years ago. I don't expect the pace of that to decrease. It was certainly stimulated and [02:36:48] highlighted by the pandemic, but it wasn't created by the pandemic.

And when the pandemic is over, it's not going to go away. So took tremendous opportunity there.

And, I'm really looking forward to that future where those trial options, and the definition of what a trial is, and what its footprint looks like is very different than it's today.

Esther Krofah: And I would say even the participate experience of what a trial is like, as [02:37:18] they're able to engage in a variety of different ways, that experience could have spillover effects that can encourage more participation in other kinds of trials.

James Mayne: Trial access is more about than just getting to the trial site. Trial access is not just a taxi ride. And, for patients, we've had these focus groups, and we've heard from patients on this, some of the things that are very important to them is being connected to the trial and having an interactive [02:37:48] way to work with the trial in between samples or in between scheduled visits. It means having direct and ready access to your own data. Very important. "I want see, and know, and understand what I'm contributing to this, and what those data look like and how they affect the broader interpretation," and all of these things are enabled, not just the access to patients, but the access for patients, are [02:38:18] all enabled by these technologies.

Esther Krofah: Yeah, absolutely. Well, I can keep going with my questions, but why don't we bring in the questions that are coming in from the audience. Dr. Kurilla, why don't we start with you. There's a question here about, as you expand to community sites and other quote, "new sites", what level of training and support is needed at the expansion sites?

Michael Kurilla: Yeah, no, that's a great question because that's what we found to be one of the [02:38:48] major limitations in terms of bringing on these facilities. And in many cases, it requires some dedicated staff, usually coming from a affiliated academic medical center, to really provide that at the minimum, some training, but typically providing some actual warm bodies conducting some of this, because many of these healthcare facilities, they simply don't have any slack or available [02:39:18] bandwidth to add stuff on top of what they're already doing. And so having that prior engagement with an academic center from past experience that really does grease the wheels in terms of moving forward, knowing that there's already a relationship, knowing that they can rely on a larger facility to back them up and provide them with additional resources should be needed, [02:39:48] I think is absolutely essential.

So having those preexisting relationships, it's not the kind of thing you try to develop in the middle of a pandemic, although we do that. If you have something well established, that is preexisting, it's no different from having that prior engagement with the community that you're trying to recruit from, that you already have some trusted partners, you already have the contacts, who to pick up the phone and call. And so, I think having that preexisting relationship

[02:40:18] is the most important. But really providing some dedicated personnel and resources to really help them get online in terms of being able to implement that protocol is absolutely critical.

Esther Krofah: Yeah, absolutely. Those are great comments, and others are welcome to jump on that as well, Barbara.

Barbara Bierer: I was just going to add that one of the challenges and the reason for needing [02:40:48] to keep these sites warm is that people are working as hard as they can all the time, and then to take on additional responsibilities in terms of the trial is really almost impossible to do in the context of your day job. So, if one expands the definition of what an investigator is, which then we have to deal with 1572s and engagement and all the rest of it, which [02:41:18] we'll assume we can do, we have some options, but similarly, we need to either provide search capacity or the ancillary staff that can take up that slack as it were when they're is an emergency, or keep those staff engaged in the interim. [02:41:48] But it's not something you can turn on and off, even if you could arrange for the academic centers to get involved in training.

Esther Krofah: Another question has come up ,similar to that, questions are emerging around pragmatic trials, and I know the next panel will talk about that as well, in how community based settings can perhaps move quickly, more quickly, on pragmatic trials than what we consider the gold standard. [02:42:18] Do you all agree in terms of how do you create simple protocol trials that can be embedded at a community setting? Any comments or reactions to that.

James Mayne: Full agreement? I suspect most of the panel panelists will agree with this statement that the ability for a new site to get up and running, and particularly perhaps community facing sites and investigators that are not proximal to a large academic facility, [02:42:48] you really do need those early learning opportunities and early relationship building opportunities with the community to have long term success. So, starting with pragmatic trials, starting with trials that require less infrastructure, perhaps, and are a little bit more straightforward in terms of the benefit risk for both the site and the patient, [02:43:18] are great. But I don't think we should limit our thinking about community facing sites to only being capable of doing those types of trials, but it is a good starting point.

Michael Kurilla: The one thing I would add to that is I think that with any interventional trials, particularly if it's for registrational purposes, there are regulatory questions that have to be addressed as a part of that trial. There are also scientific and medical questions [02:43:48] that that trial hopefully, with that intervention, will be able to answer, but then you also have just the practical applications of how that intervention is actually going to be used. And, sometimes when the protocol is developed, trying to put all of those issues that everyone would like to address into a single protocol, you end up with something that's very difficult to actually execute. And I think in the event of a pandemic, as we'd seen in an outbreak,

you really [02:44:18] want to do try to keep it as simple and direct as possible to.

PART 1 OF 4 ENDS [02:44:22]

Esther Krofah: Really wanted to try to keep it as simple and direct as possible, to answer the very critical questions that you're really trying to get at and not be comprehensive or exhaustive in the approach.

Barbara Bierer: So I second that or third that. I would add a couple of other things. One is that we need to keep the research-related data, either embedded in the electronic health record. And then that has [02:44:48] implications for what that data should look like and how it's secured and transferred and all the rest of it. I don't want to underestimate the degree of distrust in the community about government access to personal data. And I think we need to think about whether there should be some protections around that.

I'm also sensitive to the fact that in many instances, we require [02:45:18] social security number and ITIN number. Which again, excludes a certain proportion of people, or creates a concern from the very people we're trying to include. So having a much more granular understanding of what's acceptable and control over the data; ensuring privacy and confidentiality, and being genuine about what we can and cannot promise. I think is [02:45:48] part of it. And then, having the IT infrastructure to make this as seamless as possible. The data elements as important as possible and not ancillary to the work. And sort of thinking about it, going forward, in that way. But I agree, there's no either or, it's both and.

Esther Krofah: Mm-hmm (affirmative). Doug, I'll give you the last word before we wrap up.

Doug Peddicord: Well, gee, that's [02:46:18] an opportunity. Esther. So I actually really want to support the notion that new community sites are likely to need additional resources. Including, clinical research coordinators, trainers, and the like. So, I agree, I think Barbara is spot on that, everybody's working as hard as they can. So to ask them to do, kind of an additional set of tasks, is going above [02:46:48] and beyond and I think we need to think about how to best resource that. I will say, on a quick note, having sat on the board of CDISC board for over eight years, one of my colleagues reminded me that I needed to talk about data standards. That CDISC, I know in particular, came forward with a COVID 19 data standard in about six weeks time. Which I think was really useful for those collecting [02:47:18] data.

The last thing I will say is, I really want to stick with this, not either or, but both and. I think Barbara makes the point that, in going into communities where there are trust issues, we certainly need to be clear about what we can and can't do, and the uses of the data. I'm not sure that in truth, the question around [02:47:48] the uses of the data, the accessibility of the electronic health

record and the like are significantly different between those communities and the communities of people served by academic medical centers. But I think the perception is really important. I think we need to make representations to the community. That the research that we do, is in their interest. Whether it's federally funded or industry sponsored, makes very little difference. So, I just want to say [02:48:18] thanks very much for the opportunity today. It's been a great discussion. I look forward to further conversations on all of this.

Esther Krofah: Well, thank you so much. It's a great place for us to end. Barbara, you bring up some great points, says it all in terms of trust, and how do we build this appropriate infrastructure and resourcing. But importantly, how do we keep everything warm in between pandemics. And certainly appreciate all of your work in this area. There's a lot of work for us to do going forward. [02:48:48] And we'll learn from the next panel, how we can have specific tools, that can get these sites up and running. So thank you so much, Jim, Doug, Barbara. Dr. Kurilla, really appreciate your time here today and certainly all of your efforts in getting us through this pandemic.

Barbara Bierer: Thank you, Esther.

Esther Krofah: All right. Over to you, Kevin.

Kevin Bugin: Thank you, Esther. And thank you, panel two, that was just fantastic. And I made a giant note in my notebook around that question about how to keep the infrastructure warm and ready. And the note [02:49:18] that I wrote was by engaging those communities to ask them what their key needs are and use that as our starting point. So again, great discussion. So with that, we'll be transitioning over to panel three, which will be discussing, as Esther just mentioned, clinical trial execution. This panel will be moderated by Mark McClellan, the director of the Robert J. Margolis, professor of business, medicine and policy, and founding director, sorry, of the Duke-Margolis Center for Health Policy at Duke University and [02:49:48] Sarah Sheehan, the Managing Associate Director of the Duke-Margolis Center for Health Policy, as well. So Mark and Sarah over to you.

Panel 3: Clinical Trial Execution

Moderated by

Mark McClellan, MD, PhD

Duke-Margolis Center for Health Policy

Sarah Sheehan, MPA

Duke Margolis Center for Health Policy

Panelists

Samuel Brown, MD, MS
Intermountain Medical Center and University of Utah

Janice Chang
TransCelerate BioPharma Inc.

Clark Files, MD
Wake Forest School of Medicine

Monica Webb Hooper, PhD
National Institute on Minority Health and Health Disparities

Kate Zenlea, MPH, CPH
The Global Health Initiative at Henry Ford Health System

Mark McClellan:

All right. Kevin, thanks very much. And I want to give a special thanks before I get started to the Reagan Udall-foundation. This foundation is playing a critical and unique role in helping to advance regulatory science in a whole range of issues where the FDA, working with other parts of government and the public, can make a difference. And also a special thanks to Kevin and the US government team [02:50:18] that was able to put in all the effort to bring this together while also working hard on the current pandemic. And I know a whole range of other issues. And then last, all of those who contributed to part of the collective effort on developing these recommendations. Clinical trial execution here really is about bringing effective clinical trials to a much broader part and much more powerfully into our healthcare [02:50:48] delivery, particularly needed in a pandemic. When we saw a lot of unanswered questions about treatments early on, by definition, you don't have any that work and a fragmented response, despite best efforts by the federal government and many other agencies and entities to learn quickly about what treatments can work well.

And so the goal here is to accelerate and improve preparedness and response for future [02:51:18] pandemics, including making those responses more equitable by creating a clinical trial and healthcare infrastructure, that includes a broad and more diverse range of health systems and patients. So this part of the report describes the supporting steps for that, that includes changes to regulatory and legal oversight of trials. So they're fit for purpose improvements to data infrastructure supports to collect data at a bigger scale tools and resources [02:51:48] to help healthcare organizations assess readiness and help them participate in the effort, all leading to broader participation in a more coordinated, comprehensive effort to generate timely representative and meaningful evidence. And that applies, we're just talking about not just during the pandemic, but keeping it warm and addressing key related questions on respiratory illness treatments and the like between pandemics. [02:52:18] I think there are three keys to looking at the specific recommendations of this report.

First, they all tend to center on the concept of fit-for-purpose clinical trial requirements. You can maybe imagine different tiers of clinical trial intensity in

some cases, especially, for less well-understood drugs. You really need to know about rare side effects, potential mechanisms and interactions with other medications, et cetera. On the other hand, [02:52:48] in conjunction with those kinds of intensive studies and in more typical academic trials, there are a lot of cases, especially being of a pandemic where a known drug like dexamethasone, that's being repurposed. And we understand a lot about its safety effects profile already. And we're wanting to simply know, does it work in this context, perhaps a simpler approach could work. That was the logic behind the solidarity trial platform in England that was able to [02:53:18] bring in participation from a very broad range of community providers and generate a lot of useful and timely evidence on COVID response.

Second key is that this does take some policy changes, funding that focuses on platforms, broad participation, validated data collection coming from routine electronic data sources. So they're non-burdensome again with aligned payments, particularly for providers in high social vulnerability index areas that are [02:53:48] treating hard to reach populations, recognizing the importance of making this a really inclusive pandemic learning healthcare system, and third, nothing short of culture change along with that. Trust among providers and communities, including those that have been hardly reached in previous research and treatment efforts; expectations among frontline providers that answering key urgent evidence questions is feasible and can be part of their work. So I want to turn to Sarah Sheehan from Duke-Margolis to [02:54:18] provide a high-level overview of recommendations, and then we're going to go to our panel.

Sarah Sheehan:

Thanks so much, Mark. Yeah, really pleased to be here. My name is Sarah Sheehan. I'm an Assistant Research Director at the Margolis Center and pleased to walk through the five approaches to support overall improve clinical trial execution that we've pulled from this event with the help of many of the esteemed panelists on our panel today and others you've heard from earlier and throughout the day. The first recommendation and approach we see is important to achieving [02:54:48] the overall objective of meaningful participation in well-designed trials that are set up to achieve actionable results at their completion is really improved and more effective legal and regulatory oversight of trials conducted during public health emergencies. And part of this is working towards approaches that help trials and trial sites work together and collaborate and avoid competing across one another for patients and resources. We heard a lot about master protocols and platform trial [02:55:18] designs that can help with this increased collaboration across trial sites and then trials in general.

The second part of this recommendation being approaches that help larger and a more diverse group of providers and participants participate in pandemic trials. This should help us improve the representativeness of clinical trial populations and ultimately help us improve the efficiency of clinical trial conduct to help us mount an effective public health response in an emergency data collection setting. [02:55:48] The second recommendation you see on the

screen here is also aimed at improving efficiency in trial conduct, particularly through the development of reusable tools and resources that help us assess trial site readiness. So this, as you heard a lot in the last panel will help us get, and hopefully keep trial sites ready to address some of the priority researchable questions that can help us effectively respond to the data needs during future public health emergencies [02:56:18] and really in other therapeutic context where there are areas around that medical need.

The third recommendation here is actually ended, helping us identify some of these priority researchable questions and matching up data needs, especially data needs for regulatory decision-making with the capacity of existing trial sites and networks. So developing a framework like this can allow us to conduct streamline trials, hopefully going forward. That balanced data collection needs both for regulatory [02:56:48] and clinical decision-making with the data collection capacity, right? It's burdensome to carve out time during care delivery for data collection efforts. And we want to make sure to decrease that burden on our clinician investigators to boost participation in clinical trials more broadly. The second, and an important part of this recommendation here is really aimed at the engagement of community trial sites in research efforts going forward. [02:57:18] I hope our panel will talk about this, but this will be done in part by matching up data needs again, right, with the capacity for data collection and different types of sites, and may allow for different levels of data collection based on that capacity.

So really hoping to get further into what it takes to incorporate these community-based sites, which provide the most care to the most Americans, but do not participate frequently in clinical research. [02:57:48] The fourth and fifth recommendations here are aimed at supporting broader participation, as Mark mentioned. So this culture change effort to drive participation in pandemic trials. This will be supported by improved training and resourcing, especially in these community health sites that were mentioned in the last panel. They need more help getting it going. They need more help with data collection and of course, trial conduct more broadly. And this will also be supported by a broader [02:58:18] effort to embed research into routine care, helping more frontline providers participate while they do their day job.

Finally, in the fifth recommendation will be key to supporting effective, efficient, frontline participation in future public health emergency trials and in trials more broadly, but it really takes aim at the integration of research and care through the adoption of digital tools to simplify, automate and standardize data collection. Janice, [02:58:48] we hope you can help us talk through that today. And I think we had some comments in the chat about appropriate reimbursement to incentivize provider participation in these trials, as part of their day job as well. So hope to take aim at covering this broad group of recommendations with panel remarks in a second. I'll turn it back to Mark to introduce that panel. And thanks to everyone for joining us today.

Mark McClellan: Sarah, thanks for that very concise summary of a lot of material. We've got a great panel [02:59:18] with us to discuss and expand on these issues. That includes Sam Brown from Intermountain Medical Center at the University of Utah. Clark Files from Wake Forest School of Medicine, where he has been leading some of the I-SPY COVID efforts there. Monica Webb Hooper, the National Institute on Minority Health and Health Disparities. A lot of interest in the inclusive and expansive approaches that we're proposing here. Kate Zenlea [02:59:48] from Henry Ford Health System, also involved in these frontline clinical trial efforts, and Janice Chang of TransCelerate BioPharma, TransCelerate, as you all know, has been doing a lot of work to try to expand effective trial participation, reduce the cost. So we're going to start with Sam. Sam, thanks for taking time out of. I know, is a pretty tough surge right now in Utah.

Samuel Brown: Yeah. Thanks Mark. Thanks for having us. And I have to say this has been an awful pandemic [03:00:18] in so many respects, but one way it has not been awful is the opportunity to work with so many of you and so many other good people like this. As we try to come up with good solutions. I'm coming primarily now, as someone working, I'm the Senior Medical Director for clinical trials at Intermountain Healthcare, which is a large and expanding regional and now multi regional healthcare system, but I'm also a clinical trialist and have been for some years, and I'm chair [03:00:48] of the active three B protocol for critically ill patients, and the PI for the PETAL Network Utah Center. And so I've been thinking about it from both of these perspectives, and although I'm not here to formally speak on behalf of Intermountain, in these quick comments, I'll be thinking about what it's been like at Intermountain.

And I think most of us remember early 2020. I think some of us still worry that we're still in April 2020. [03:01:18] It's just been stretched out in some kind of quantum nightmare, but we were faced at Intermountain Medical Center with the beginning of a pandemic that was coming hot and heavy. The realization that the formal trials would not be really ready to go active was many months off in the future and PETAL, we were working very nimbly to launch orchid at pandemic timelines, but we realized in Utah that we had a movement that's now actually been litigated in criminal court, but we had a movement [03:01:48] to make hydroxychloroquine available without a doctor's prescription from a giant warehouse full of imported raw API. And we felt like we could do better as a state. And so there was a moment where all of Intermountain leadership assembled around doing a pragmatic comparison of hydroxychloroquine azithromycin at all of our hospitals.

And we did it knowing full well that on its own, it would not have adequate power to identify a relevant effect; [03:02:18] but we also were careful to synchronize it so that it could walk into an individual patient meta-analysis. And in fact, it has done so, and crucially, even though I think it would've been listed as one of those problem trials. It allowed us to galvanize the attention of executive leadership, clinicians and all the people who wanted to help out in a way that was incredibly important to the success across Intermountain of not

only that trial, but of many trials to follow. [03:02:48] And we went quickly with the first trials that looked scientifically rigorous and were available to run. And so we had a mix of pharma and PETAL, and then we moved as active, became mature to a predominantly active-based platform. And as we've worked this through, it has occurred to me that you really need three core things to make this work at these hospitals that are not traditionally academic.

You need stories that work for people [03:03:18] that we've been calling it, culture change, but culture is complicated, but a key part of it is the capacity of participants to understand themselves and the work they do in a new and helpful way. And you need systems that don't get in the way. And that's something where I think we in the community assembled here can make some progress, and then you need relationships that nourish. And I think all of us, if we're not already mindful of it, need [03:03:48] to be of the fact that you can only get so far off platitudes and mega-stories. There needs to be a bit of chemistry with the groups that work together. And as we've worked through within NIH, within the act of three family, that's brought together preexisting networks from both NHLBI and NAID. We have noticed that what really has sustained us is the fact that there are these core groups that know, and like each other and that have been working together.

And then it's almost like the two families [03:04:18] meeting at a wedding and figuring out the relationships together. But if you don't have that, you're not going to be able to pull things off. In terms, quickly, of the stories that I think we need to have in mind is what do good clinicians do? What do they do? Historically, we've said they treat, but I think they need to respect, treat and learn. And that needs to be a sense, a shared story, that this is what clinicians do. They respect, they treat, and they learn. We also need [03:04:48] a story and we've done a very good job, I think, at Intermountain of this. Of understanding, what do you do with experimental therapies? Do you get t-shirts and protests and access without a prescription, or do you channel them through randomized, ideally platform trials, where some patients will receive a placebo.

I'm a placebo fan, and I think they can be pulled off more easily than people give them credit for, but some people will be making a contribution [03:05:18] to the broader community and the rest will be receiving access to these experimental therapies that people are interested in, in a much safer and more rigorous way than they would otherwise. I think we also need to be very attentive when we come at it from these big groups of the story of what research is for. There's a very prominent story that says research is for extracting money from sick people and putting it into pharmaceutical executive bank accounts. And if we don't have a story, that's true, it needs to be a true [03:05:48] story. But if we don't have a true story about what it means to work together as a community to find solutions that will benefit that shared community, then I think we're dead in the water.

And I think the communities are going to laugh us off and say, I don't want to give. I don't want to be a cog in the wheel of a 100 million dollar salary or

payout to somebody. And we need to think that one through. In terms of systems that get in the way, this is where I've done a lot of work and thinking. And fundamentally, these systems are designed [03:06:18] to take care of their patients as responsibly and safely as they can; that's their mandate, and that's what they focus on. So if we're asking them to expand that capacity, we need to be mindful of what the vulnerabilities will be and what are the risks that they're needing help to manage. Some of those risks are patient safety. They want to make sure that the molecules that are being brought in to provide trial access to their patients are not going to be the next thalidomide.

They want some reassurance that [03:06:48] people are carefully thinking, vetting, and prioritizing. There's a lot of stress and payrolls right now. We've seen this across both at Intermountain, and then working on the active three-B side, trying to help people staff up. Payrolls are hard, and these systems that need to focus on providing the clinical care of their patients are not comfortable with large payroll expansions. So NIH has been very nimble, and I really want to take my hat off to the people, working with inactive on the NIH side at figuring out ways to have contract [03:07:18] supplementation. There's reputational risk; there's staff morale. And that we found that we got about six to 12 months out of people before they got severe pandemic burnout from working too much. There's only a small subset of the people in these systems that are willing to be the nerd workaholic who works just out of the pure passion for science.

There needs to be some awareness of their work-life balance, and how to achieve effective trial participation without [03:07:48] destroying it. Regulatory compliance is a big deal. And I don't say it to be kind of classic or rude, but the only two times I've seen my research staff cry are when a patient is inexplicably angry with them, or when they've had a rough visit from a monitor. And I think we need to acknowledge that some people call it with just a little touch of cynicism, the regulatory-industrial complex. I think we need to be mindful of the times when [03:08:18] that system may be serving ends that feel at odds with the ends that the people being asked to participate in trials are encountering. Indemnification, I think we know is a big deal; people are working on it. You're asking somebody who does 99% clinical care delivery to carve out a little 1% with an unpredictable, and as yet unknown risk of a spurious lawsuit.

They will want some understanding that that will work out okay. And then in terms of the relationships that nourish, [03:08:48] I think again, PETAL has been a core at Intermountain for a long time. Intermountain was one of the founding members of [Artsnet 03:08:55] that then became PETAL. And through PETAL, there were pre-established relationships of people that liked each other and worked together well, and it was very natural to then expand it out. So there has to be some core, some sense of identity that people are tied to that makes it possible for them to then be nimble and flexible. And as we talk about these huge platform trials, I think it's going to be important to realize that people are, [03:09:18] at some point, not going to be interested in carrying the water for somebody else. There's going to have to be some sense that different groups or

different sub-networks get to be in charge of a thing, even if the overall infrastructure stays the same.

And again, speaking from my own experience with the active three family, that's something that's really come off quite well with that sense of sharing and moving around. And the last thing I'll comment on is that I think we need to think very carefully about the MD centric model that we've had for so [03:09:48] long, these 1572s, the sense that it's all about the MD and the core investigator, and recognize that, for example, we discovered that the antimicrobial stewardship pharmacists were by far the best early entry into having investigator boots on the ground at the various hospitals that are not accustomed to doing research.

Hospitalists, for example, clinical hospitalists, if you can carve out a little bit of administrative time for them, can also be a helpful group. And I think fundamentally what [03:10:18] would be most useful for the systems managing that risk for them of making sure these are good molecules that the payrolls can be, be done, but it's not going to interfere with clinical work and then figure out what are the discrete quanta of support that are required to maintain a throughput for say, two years. If you can walk to a system and say, we would like to provide you the infrastructure money, some capitation incentive to... [3:10:48] that's fine.

That will allow you to have this quantum that's needed to maintain trials open in this location for two years. And these are the trials, and they're vetted. And you're welcome to have a representative on the steering committee. I think that's a much easier lift than the usual multi-emails from the CROs recruiting, or even from the network saying, here's our little protocol. How do you want to sort of integrate that together? And on that, I'll turn it back to Mark and the other [03:11:18] panelists. Thank you for your attention.

Mark McClellan: Thanks very much for those very insightful comments, Sam. Next, I'd like to turn to Clark Files.

Clark Files: Thanks, Mark. Clark Files, I'm really happy to be here. Always a tough act to follow Sam. I've worked with Sam over the years. It can come at this, with the perspective of a critical care physician here at Wake Forest and a clinical trialist [03:11:48] and basic scientist, which has been hard to do during the pandemic taking care of people and running clinical trials. So I really wanted to focus on maybe four to five concrete points that I think are tools and areas where we could improve our clinical trials execution. So the first, and some of these Sam has mentioned, [03:12:18] but maybe I'll elaborate a bit. So first, in, clinical trials contracting continues to be challenging and tends to be one of the major hang ups and slowdowns that we have for getting study medications to patients.

We need a national way to standardize these, streamline them, and for teams at sites [03:12:48] to make it really clear to the lawyers, what it is we're doing and what it is we're not doing. And to just give one concrete example. Last week, I

had a contract for a multi-site trial that was getting delayed for a few days and spoke with my contracts' team. And they were going back and forth. We were at site, not the primary site, for a clinical trial. They were going back and forth about how they wanted us to retain rights, to publish data [03:13:18] on the 10 or 20 patients. We may enroll in each trial, right? Not important, not an important thing and not my intention. So little things like that tend to be where some of these processes get hung up. And I think we can do better.

The second, which has been discussed quite a bit, is the IRB. I think the movement towards the central IRB over the past four or five years has been a major improvement [03:13:48] in clinical trials activity. And I think during the pandemic, we've seen really successes, both with private central IRBs and academic central IRBs. They need to have track record of doing this kind of work, being efficient and working the sites to get them going. They think we have a number of models and examples of that during the pandemic. Another point I wanted to make, which I haven't heard [03:14:18] spoken about on today's panel is infrastructure and support for pharmacy, particularly in the area of inpatient clinical trials. Investigational pharmacy is a unique field. And I would say, I don't know data on this, but if you look across the country with my experience with operations in the I-SPY trial, many sites don't have investigational pharmacy or their [03:14:48] investigational pharmacist is very thin.

We need to have more attention paid to investigational pharmacy. We need to find ways of standardizing things like order sets and getting investigational drugs operational at sites. Many sites have similar electronic medical records, yet the way to operationalize those order sets differs and sometimes can take weeks [03:15:18] and weeks to get activated. It seemed like sort of low-hanging fruit for us to challenge the system here a bit. The last point, which I think has been mentioned quite a bit, that I think this group should really think about is training the next generation, right? So many of the people that are conductive, we're investigators and continue to be investigators in these clinical trials, are frontline providers. [03:15:48] Lots of people have been working hard during the pandemic. It's been the best of times to be an RDS researcher. There's been more a RDS in the past 20 months than there has been in the last 100 years.

But we need to realize that there needs to be new pathways to train clinical trialists, maybe that can go out and support these sites, that could be through a variety of different [03:16:18] training paradigms, could be PhDs, could be master's level, could be MDs, could be advanced research coordinators. Who've spent a lot of time at sites and have a lot of deep expertise in clinical trials execution. So I think we should think about that pipeline. And then the last point I'd like to make is many of these items we need now. We are still in the pandemic; the pandemic's not over. And [03:16:48] I think, there are a lot of these things that we could work on now, and that are not long-term goals. I think, we could work on these issues and improve the clinical trials landscape immediately. And thanks a lot.

Mark McClellan: Clark. Thanks very much. I appreciate your point about making sure we're applying these learnings to the situation we're facing right now as well. Next is Monica Webb Hooper.

Monica Webb Hooper: [03:17:18] So good afternoon. I am delighted to be-

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Monica Webb Hooper: Good afternoon. I am delighted to be a part of this important conversation and with such an esteemed panel. I want to thank you for the invitation to participate and thank Dr. Collins, who I believe, made the recommendation to include the voice of the National Institute on Minority Health and Health Disparities, where I serve as deputy director and our focus is, in part on engaging populations with health disparities in clinical and behavioral [03:17:48] research. We know that it is possible to have and to retain sufficiently diverse participants in clinical trials, and in my pre-NIH professional life, I conducted behavioral clinical trials and translational research with largely low socioeconomic status and also racial and ethnic minority individuals. I approach this topic of clinical trial execution from that perspective and experience also. And [03:18:18] we know that this is a long standing concern in terms of the underrepresentation of racial and ethnic minority groups into clinical trials.

We know that the enrollment fraction of racial and ethnic minority patients in funded trials and our age-funded, industry sponsored-funded trials for cancer therapeutics treatments for kidney disease, many others, under represent U.S. patients and the reasons for underrepresentation, I would argue that all or at least [03:18:48] most are addressable with appropriate resources and efforts. I think one important factor that reduces inclusion that trialists have much control over, and several studies have shown this, is that the narrow inclusion exclusion criteria of RCTs may have the unintended consequence of excluding the most vulnerable participants, such as the medically underserved, [03:19:18] those with comorbidities or groups who experience disproportionately greater health risks, and mortality. And as such findings may have limited generalizability to these populations. And this also has implications for health equity.

The discussion in the scientific literature about the lack of diversity and biomedical research trials is all too often, one sided. What I mean is that most of this work has focused [03:19:48] on individual level reasons, often sort of pointing the finger at individuals. Statements such as, "Minorities don't want to participate", or "They have distrust", or "They are good compliant participants". Often and left out of the discussion and the data are the upstream social determinants that not only affect health, but also clinical trial diversity and inclusion. That is to say while at first glance, these seem like it's all about individual choice, [03:20:18] the reasons, and I would argue the solutions are not all about individual choices or decision making. And that's why it is important to understand and bring social determinants into this conversation and helping people define social determinants of health as the conditions in the

environments, in which people are born live, learn, work, play, worship that affect a wide range of health functioning and quality of life outcomes and risks. [03:20:48] Healthcare, and not just healthcare access, but access to high quality healthcare is a critical social determinant of health.

These determinants also affect one's ability to participate in clinical research, even when interested in doing so. For patients seen at oft, under resourced, safety net hospitals, options for joining clinical trials are limited to non-existent. And even among racial and ethnic minority patients seen at private [03:21:18] and university-based hospitals, there are biases that I've witnessed personally, and that you can read about in literature that prevent patients from being offered opportunities to join trials. Concerns and judgments about who might or might not be a good participant, who may or may not be compliant. And who may or may not adhere to a list of, often confusing instructions. For patients who speak a language other than English materials and consent forms describing the trials [03:21:48] are often unavailable and staff who speak Spanish and other languages are often not on the team. These are social determinants and the goal is for everyone to have, these are opportunities for participation consistently.

One means to help us with this is to really think about the role of specific social determinants in clinical trial inclusion, for the purpose of using these data to implement policies and best practices that support positive multi-level change. [03:22:18] This is how we can improve representation and do so in sustainable ways. I think the good thing about some of these social determinants is they're modifiable. That means we have opportunities for change. The last thing I'll point out is that we know this is not a new issue in terms of diversity, but I think the health and the other disparities highlighted and exacerbated because of COVID 19, has re-energized the attention to the inclusion or lack of inclusion of racial ethnic [03:22:48] minority persons into clinical trials. I've never seen so many media stories on this issue. And COVID 19 created a long needed window of opportunity to focus on improving the overall lack of diversity inclusion in trials.

And even if you look at the pandemic as an example, national data from the CEC, which indicate persistent disparities by race and ethnicity, the inclusion within clinical trials demonstrates the importance of having an infrastructure to support enrollment across [03:23:18] a range of diverse backgrounds. And as I heard on the last panel, this concept of being warm and ready, I really like that. If we don't have in have this all in place before public health emergency, then we're going to be playing catch up in terms of diversity of enrollings. The same applies to any area of clinical trial conduct. If we are not ready, we will be playing catch up and we may fall short of our accrual targets. Thank you for allowing me to join this meeting. It's important. And I think the goal minimally, [03:23:48] I would say, is to have representation in trials that match the U.S. census, which has just been updated by the way. But the real goal is to have representation that matches the burden of the disease or condition. Thanks.

Mark McClellan: Thanks very much, Monica. Really appreciate your comments. Next, I'd like to go to Kate Zenlea.

Kate Zenlea: Hi everyone. Thank you so much for having me. My name is Kate Zenlea. I'm the managing director for the Global Health [03:24:18] Initiative at Henry Ford health system in Detroit, Michigan. And I think where I can provide some insight and some unique experience on is, we are physically located in a city that is 80% African American. While we are an academic institution that have been participating in several clinical trials throughout the years, we don't necessarily have a clinical trial wing or building set up at [03:24:48] Henry Ford to accommodate such large trials so quickly. We had a really unique experience of enrolling a diverse population, as well as really building the infrastructure from the ground up for a clinical trial of this magnitude. We've run two of the phase three COVID 19 vaccine trials for Moderna and Johnson and Johnson, where for Moderna, we actually were the second highest enroll site [03:25:18] in the country.

And some recommendations that I would have, or experiences that we really had to navigate through was certainly in terms of the tools and the systems that are needed to set up a clinical trial. From the beginning from site activation we were always provided did regulatory material, right at the beginning, months before we were going to start, however, training materials, SOPs, site access [03:25:48] forms, site blending plans. Those were really only provided to us at the very end. And we of course, had a team where we had clinical trial coordinators and research coordinators on the team. But again, a lot of our staff really didn't have this background per se. We were pulling from, especially given the staffing shortages that we've seen throughout the pandemic. We were pulling nurses who had been in [03:26:18] the ED not necessarily had been working in research in this capacity.

That took us some time to get up and running. And again, the sooner we could get those materials and standardize them the better. Secondly, in terms of the system that we set up, we found that enrollment, especially for a public health emergency and one where we're dealing with a novel coronavirus is not going to be a problem. Everyone wants to enroll. There's really [03:26:48] not anyone who did not want to enroll in this trial. That we didn't have any problem getting enough eligible participants that were interested in rolling. Where we did see some trouble was setting up all of the other perfunctory roles that were necessary for us to operate. When we put out the call that we were enrolling for this trial, we then had to make sure that we were set up to field, the thousands of inquiries that were coming through, the call center, the scheduling, [03:27:18] all of the data software that was necessary to manage this large influx of participants.

And again, in order to enroll more participants, that's going to be an exponential mass problem essentially. If you enroll a smaller number of participants, given the protocol schedule of when follow up visits need to happen, of when safety calls need to happen. You can probably manage that pretty [03:27:48] easily

without having such a sophisticated software up and running of when participants need to come back within their study visit window. However, when you've enrolled thousands of people that can get really tricky really quickly. You need to make sure that your research databases are up and running. And I know others have mentioned this in terms of the integration and the data sharing between a research study database and other [03:28:18] medical records that already exist. A lot of the information that we were collecting was already available in other medical records that wasn't necessarily linked to the research study.

If there is a way to kind of integrate those two, I think that would save a lot of time from that perspective. In terms of digital tools, while digital tools are helpful and obviously are the wave of the future. For the population we were working [03:28:48] with there were a lot of our participants where this really was not an option, whether they did not have smart phones whether they were distrusting of digital tools, even from looking at the consent form. We found that what put more participants at ease, really just to have a paper copy of the consent form instead of having them sign something on an iPad that they weren't necessarily comfortable with, especially when they're trying to make the decision whether [03:29:18] or not to participate. Beyond that we found that a lot of the recruitment methods especially regarding minority populations, it really was us to just target physical outreach to these populations, work with faith based and community based organizations.

And of course, building trust with those community partners. This obviously takes a lot of time to build and in the wake of the public health emergency, there wasn't a lot of time [03:29:48] on our side. It was really important that throughout this whole process, we tapped into existing trusted partnerships that we've already established and also continued to engage with new partners. And we did a lot of Lunch and learns and just talked to them about what it meant to be part of a clinical trial. Again, working with these minority populations with the low socioeconomic status, a lot of them don't even know what a clinical trial is. That they even exist, they're available [03:30:18] for this types of population. And another thing that we did find in terms of retention of minority populations that we were enrolling was specifically regarding educational efforts. Really directly addressing fears and drawbacks, instead of just dodging these questions and pretending that our modern day monitoring or review boards have it covered at this point.

[03:30:48] If there's one thing that's certain is that politics is alive in science, more than ever now, and these communities are aware of that. And there's really no way of facing that reality without having that honest dialogue. This is to talk about the history, talk about the abuse, talk about the frameworks and legal codes and guidelines that have really come out of this suffering and what we are able to do to make them feel comfortable. Again, of course, marketing and [03:31:18] targeted communication is really important for these communities as well. And really understanding that a lot of our participants receive information in different ways. It's really important for us to figure out

how these communities receive their information and to work with them. And then in terms of staffing and resources, the last point I'll make for that is when you're enrolling a diverse population, it might take extra staffing and resources to keep these participants into the trial.

[03:31:48] We of course found a lot of non-compliance with such a transient population. That means we'd have track people down and call them, remind them that they need to fill out their e-diaries and so on and so forth. And this is definitely important to bake this in to the cost structure, to the payment structure. We were hiring an entirely new team, as many people have mentioned here, everyone is working at full capacity. We weren't pulling from existing resources. We were hiring new [03:32:18] staff that we were paying for, out of pocket, until reimbursements came through.

And that took a lot of extra time [inaudible 03:32:26] that really needs [inaudible 03:32:28] that realistically are going to have to spend more time with data collection, data entry, non-compliance to keep these people engaged in the trial. And once we do reach them, they want to be in the trial and maybe they just needed a little bit of extra direction or they [03:32:48] needed the reminder that they had to enter this information in, but certainly their heart was in the right place. With that, I'm going to pass it back to you Mark. Thank you again very much.

Mark McClellan: Okay. Thanks very much for those very insightful comments and next I'm turning to Janice Chang.

Janice Chang: Great. Thank you, Mark and good afternoon everybody. My name is Janice Chang and I'm the chief operating officer at TransCelerate and big thanks to Reagan-Udall foundation for including [03:33:18] me and part of the TransCelerate voice to be a part of this afternoon's discussions. And I would say that it's a real delight to be a part of the panel. It's definitely even a special treat to be the last panelist introduced after a whole afternoon of discussions. For those of you who may not be familiar TransCelerate is a not-for-profit organization. And our mission really is to bring together, not only sponsors, but really also proactively engage with stakeholders [03:33:48] from all over the world to collaborate and find ways to simplify and accelerate the way we conduct research and development activities with the ultimate aim to really find ways to bring those innovative medicines to patients all over the world in a more efficient manner.

And our core principle in TransCelerate is that we really focus, since our inception in late 2012, on developing pragmatic tools and templates and processes and [03:34:18] technology solutions that can be widely available to the public, the broader ecosystem for everyone to adopt and benefit from. And as I joined sort of this walk down memory lane and reflect on what we have observed over the past 18 months since the pandemic hit, I will probably say the first and foremost, we really saw all of us really kind of really rose to the core of action, right? We really banded together in my mind as sort of [03:34:48]

citizens of the globe. We had this unifying problem that particularly as professionals in our industry really had an obligation to do our part individually and collectively to come together and find ways to really tackle the challenges that we experience.

I thought maybe I would start off by sharing some of the activities that we did as part of TransCelerate, mobilize some activities and in response to the pandemic. And then also share some of my perspective in [03:35:18] some of the challenges we experienced as part of executing some of those activities. First and foremost as I said, we saw truly, I think even Dr. Winckler in her opening remarks, mentioned that we really saw unparalleled degree of willingness to share and collaborate. I think those early weeks, almost immediately we had, across the 20 sponsor companies as part of our membership, we had on a weekly basis sometimes almost multiple times [03:35:48] a week, hundreds of leaders from all over the world coming together, really sharing the evolving guidances from different countries. And also when we think about how to form a trial continuity perspective, exchanging learnings and best practices, how do we continue to get the treatment to the patients and to make sure that we maintain the trial continuity in different regions of the [03:36:18] world and really kind of sharing what worked and what also didn't work.

That was really, really encouraging to see in those early days. And we also saw, I would say within the first few weeks, multiple health authorities reaching out to us proactively as TransCelerate. And I think it's sort of, we're in a unique position because we're a not-for-profit and we are a group of 20 sponsor companies with one united voice, and an opportunity in those discussions to really [03:36:48] co-learn, I think that's from one particular health authority saying, "How do we navigate through these challenges and disruptions that we're all experiencing?" It was really encouraging to see that kind of sentiment from multiple health authorities, not just FDA in this case, but really kind of just really banding together to try and tackle this problem. And unilaterally we saw that can-do attitude, right? I mean, I think that we saw what can happen and think that when you think about [03:37:18] the treatments and the vaccine's development, what can happen when we really think out of the box and the willingness to perhaps adopt different tools and methods and processes in times of crisis.

And as TransCelerate we were first and foremost, one of our first activities was actually to pull together an inventory of many common tools and templates that I made available to Active and FDA. That could be to potentially leverage as part [03:37:48] of the different trial activities. And then we also working with COVID R and D's, the organization that you guys heard from the first panel, and also then kind of worked together to launch a data sharing module as part of our data salary platform. And there was open access to not just TransCelerate member companies, but also it was open and available to qualifying smaller biopharma companies there. It's an opportunity to really share data in real time. And then we also [03:38:18] developed true to TransCelerate's principle. We developed some tools, pragmatic tools, right?

We made available a protocol deviation toolkit, which came in pretty handy. And we also created a set of considerations for CSR in related to COVID-19 disruptions. Again, those are just some of the practical tools that our member companies quickly came together there and develop and made available for [03:38:48] the broader ecosystem. And I think when I think about the future and where we are, right, I mean, the reality is the future is here. We have an obligation not to go back and out of necessity, particularly in the clinical trials execution space, we saw adoption of many, many novel nontraditional tools and especially digital technologies in order to maintain [03:39:18] trial continuity, as I mentioned. And it did demonstrate that more could be achieved when there's willingness to work together, including the regulators and think out of the box.

But when I think about adopting those tools and non-traditional methods, I think it's perhaps particularly from the learnings now, the accessibility of those tools, right? And the training for those tools. We have to make sure they're widely available to ensure that they're actually, at the end [03:39:48] of the day, being utilized appropriately. And when you think about the assurance, what confidence of those tools, right? The qualification or validation that's necessary of those digital technologies. For the past 18 months, in those early months, there was limited guidance on how could tools be utilized. And that was really challenging. And I think that's probably something when we look forward, it's [03:40:18] an opportunity for us to proactively put some of those requirements or guidances in place.

And then I think about the older, different privacy requirements, when you think about data collection and though they vary region, to country to country, right? And it's really challenging at a global trial level. How do we ensure that those are taken into consideration proactively? And then last but not least certainly, I would say we are not sure on new tech [03:40:48] technologies. We have many, many options that's out there. I do think that as we have seen from the experiences, what's really lacking is probably a holistic data collection framework. And how do we kind of make sure that at the end of the day while we may be using new tools to collect and new data sources, how are we thinking about collecting those data and integrating those data from an end-to- [03:41:18] end perspective? That we can have a seamless ability to report and analyze the data the end of the day.

That's really still, I think, lacking. And I think it's very much an opportunity for us as we look forward to the future. And I will say, where we are, it's probably opportune time to really focus on clearly modernizing trial conduct, right? And how do we [03:41:48] do things very, very differently in the future, but really focusing on the importance of fostering a dynamic data ecosystem as we kind of describe it in the TransCelerate world, right? It's not about generating more data, we're using more technologies per se, but how do you really make sure that there's a framework so that we can have robust and harmonized way to collect the data and integrate the data so that we can optimize the data accessibility, [03:42:18] the data utility and the data interoperability whilst, very

much addressing the various regulations when it comes to data privacy concerns.

To conclude, I would just say we have to we're in this together, right? As within TransCelerate, we often say, "If you want to go fast, go alone, but if you want to go far, let's go together". And we, I think Sam said that we are not out of this pandemic yet, or was it [03:42:48] Clark that said that? And we still have a lot of work ahead of us. And I think the goal here is, as we heard throughout this afternoon, how do we take all these lessons learned and turn them into robust action plans so that we can take a multi-pronged approach so that we can maybe not pandemic-proof ourselves, but we can be a much, much more ready position when the next public health emergency hits us. With that, I'll turn it back to you, Mark.

Mark McClellan: Thanks very much for the comments [03:43:18] Janice. I think your last comment about kind pulling together a lot of what we've discussed in the panel about the opportunities coming out of this pandemic experience to really move forward on modernizing trial conduct with a data ecosystem, the capacity for learning conducting trials, that's much better integrated with routine clinical care, seems really important. We are about out of time. I was wondering if I could go through comments from the group. I had some great question from the audience about [03:43:48] how to do multiple arms in a trial effectively, how to implement placebos, Sam, picking up on your comments, finding ways to, building on the comments from Monica about getting trial participation, is much more representative at least of the U.S. population. If not, as in this case, of the population most affected by the disease. We appreciate any [03:44:18] quick comments you have about what's most important takeaway for where we go from here. And maybe Sam, I could start with you?

Samuel Brown: I think what we really need is a rigorous modularity. We need to be able to have, fit for purpose modules that are a regulatory environment, a kind of molecule, a relevant context for it, and the staffing and support needed for it, and then to Clark's [03:44:48] important point have contracting and legal range around it so that you get a thing that is trial of type D and you know what that means, and it's funded for what it needs and you slot it into the system. I think rigorous modularity is what we need back to you.

Mark McClellan: Thanks Sam, Clark?

Clark Files: I would really echo what Sam said, adding really a push [03:45:18] to leverage what we have done in this country with electronic data records, but incorporating data capture in a clean and pragmatic way that's useful to feed into electronic case report forms for clinical trials. The technology is there, right? It's just we need to make it do what we want it to do.

Mark McClellan: [03:45:48] Thank you, Monica?

Monica Webb Hooper: Sure. I guess I'll offer a couple of recommendations in terms of increasing representation of underrepresented groups and trials. I think one recommendation would be for clinical trialists to rethink the methodology, particularly the inclusion of exclusion criteria. There are R and D trials that necessitate the inclusions that are set for safety reasons. But I think the point is that many times [03:46:18] these criteria can have unintended consequences of excluding certain groups by design. I think a move toward more transdiagnostic intervention trials could be an intervention, an innovation when possible, also avoiding kind of automatic cut and pasting of inclusion exclusion criteria that were used in previous studies. I think the staff should be trained to focus on the factors and the protocol that motivate individuals to enroll in trials. These can be found [03:46:48] in the literature or someone can follow up with me if you'd like more information. Think about also ways to be as flexible as possible in terms of addressing the social determinants of health, not only transportation, which I know was mentioned earlier, but also other barriers that could reduce patient-level reasons for patient-level Participation.

Mark McClellan: And then as you said, making it easier for patients to participate in care systems too, along with the trials and [03:47:18] those narrow exclusion criteria, which I know people worry about, because they don't want to get a heterogeneous estimate, sort of the opposite of where we want to be, especially in a pandemic and learning quickly about treatments that could be relevant to a wide range of people. Thanks very much Monica. Kate?

Kate Zenlea: Hi. Yeah. Just to kind of echo a little bit of what Monica was saying, especially in terms of inclusion exclusion criteria we found, especially in Detroit, [03:47:48] one of our largest ethnic populations here is Middle Eastern. And in some of our studies we found that was not even an option for when they were filling out their pre-screening form to even be eligible for the trials. And then as we know, we saw in a lot of the phase three COVID trials, at a certain point, our sponsors were closing down enrollment to anyone who was not a minority. And we actually ran into trouble where [03:48:18] we were told that we could not enroll one of our largest minority groups when it was only for minorities because they didn't have that as an option and many Middle Eastern people of middle Eastern descent.

They actually select white when they fill out these forms. Just to kind of think about those nuances, it seems pretty silly to us, that one of the largest minority groups was not able to be enrolled, when it was only four minorities. These are just things that, again, you really [03:48:48] need to go to the communities and see, of course we have Hispanic and African American, but there are other minorities too that maybe aren't being fully represented.

Mark McClellan: Yeah. And if you're not prioritizing inclusiveness, we're really not going to get it there in terms of...

Kate Zenlea: Exactly.

Mark McClellan: Broadbased trials that give us representative evidence, Janice?

Janice Chang: Yeah. I'll go back to, I think what Sam brought up. It's about building trust, right? And there's so many different dimensions. I mean, building trust when it comes to technology and data, you got to have [03:49:18] robust processes and framework in place, but perhaps more importantly, I think what Monica and Kate have touched on trust doesn't just happen. We all know that, right. It's that human interaction and there's a lot of work to be done there. How do you build trust with the patients? How do you build trust with the clinicians within the community space sites? There's a lot of work there to be done, right? And I think that's, hopefully to me, something where we just got to kind of put on the top of the priority for all of us, regardless of [03:49:48] which sector of the ecosystem we work in.

Mark McClellan: All right. Well, I want to thank you all, not only for some great perspectives and reminding us that, especially at the end of the session, of what we're really here to try to accomplish. If we want to transform clinical evidence development, both for the next pandemic and hopefully more broadly in the clinical trial enterprise and especially for taking the time out to work on all this. I know you're really busy and you're where the rubber meets the road, all of these goals and aspirations for our clinical trial [03:50:18] system. You're the ones who are out there doing it. Thanks very much for the.

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Mark McClellan: ... system. You're the ones who are out there doing it. Thanks very much for the thoughtful and well-organized feedback on how we can do it better and move forward from here. So Kevin, I would like to turn back to you. The panel went over a few minutes, but I think some really good perspectives.

Kevin Bugin: Thanks Mark. I'm actually going to turn it over to Susan and she's going to move us into the public comment portion of this meeting. I will just say that [03:50:48] that was a fantastic panel. I have been trying to summarize takeaways throughout the day, so that I will be able to share them back at the end of the day, and I could not fit them all onto the one slide that I was trying to do, so there were a lot of takeaways, which I'll be glad to share later today. So Susan, I will turn it over to you and you'll be kicking off our public comment period. What I think we'll do is we'll keep to the same amount of time for the public comment, and I'll be just briefer in my final closing remarks.

Public Comment

Susan C. Winckler: [03:51:18] That works, great. Thanks so much, Kevin, and to all of our panelists. So I was thinking, in our masterclass of COVID-19 lessons learned and thinking about the prioritization of therapeutics, then the resourcing, and then the

executing of clinical trials, we've certainly shared a lot of information that is relevant in learning [03:51:48] and preparing for the next pandemic. But particularly this last panel, incredibly relevant to improving how we do clinical trials and the reach of our clinical trials and making sure that we have inclusive clinical trials.

We're now going to move to the public comment portion of the meeting. This is for those individuals who registered to provide public comment. I'm going to call on those registered commenters in alphabetical [03:52:18] order, by last name, and then we will open your microphone so that you can speak. We had the number of folks who registered for public comment. We did the math and that requires then that you have about 90 seconds to speak. We'll have a timer that will give you the 90 seconds. I'll give you a verbal warning, oral warning, at 20 seconds and then your microphone will mute at 90 seconds. I'll note that [03:52:48] neither the FDA foundation nor the agency will respond to the public comments. This is really just for individuals to provide a comment. Then we will go to the next comments. I'll note, as we said, at the beginning of the meeting, that there will not be any responses or information provided related to pending or potential regulatory action. So, let's get to the public comment and we will test [03:53:18] this out and see how the system works. I'll note, again, I'm going to go in alphabetical order, by last name. We'll give you about 10 or 15 seconds to start speaking. And if you don't respond within that time, we'll move on to the next one. It will be audio only, no visual, but let's prepare.

Our first speaker who is registered to comment is Rachel Abu Taleb. Rachel... Rachel, [03:53:48] I see you on the screen and we've given you the ability to unmute. If you would unmute, I believe you can speak. I believe you can speak and you'll be heard.

- Rachel Abu Taleb: [03:54:18] Hi, sorry about that. I'd just like to thank everyone. This has been a great afternoon of a lot of learning and I hope I even get the recording of this to catch a few bites that I missed. Just thank you very much.
- Susan C. Winckler: Okay, [03:54:48] and we will go to speaker number two, Edward Allera. Could you... There it is. Thank you for restarting the clock. Do we have Mr. Alara pulled up in the ability to unmute? Okay, Mr. Allera will not be speaking. [03:55:18] Next on the alphabetical list is Andrew Bates.
- Andrew Bates: Thank you so much to the group. I'm an acute care hospitalist. I take care of patients, critically-ill COVID patients. I was just wondering, I've read promising data regarding a medication of ariprazole acetate. Are you aware of any trials that it's involved in? [03:55:48] I'm struggling right now because we have patients that are unfortunately very sick and on a daily basis, I have patients passing away with COVID on high flow nasal oxygen and while encouraging vaccination, I struggle with finding therapeutics that are effective for them.
- Susan C. Winckler: Thank you, Dr. Bates. We'll go now to Sherna [03:56:18] Bell, Sherna Bell, B-E-L-L. Okay. We will move next to Ivory Chang, Ivory Chang. [03:56:48] We'll move

next to Jay Conway, C-O-N-W-A-Y, Jay Conway. To Nevin Dabbousi, D-A-B-B-O-U-S-I, Nevin Dabbousi. Froucke [03:57:18] De Haan? Farouk De Haan. Okay, we will move to Gere diZerega, D-I-Z-E-R-E-G-A, and I apologize if I have [03:57:48] mispronounced your name, last name D-I-Z-E-R-E-G-A. Okay, moving to the next. Steven Feldman, F-E-L-D-M-A-N. Steven Feldman. [03:58:18] Dave Hone, H-O-N-E, Dave Hone. All right, Abhay Kenjale, K-E-N-J-A-L-E, Abhay Kenjale. [03:58:48] Yasmeen Long, L-O-N-G. For those of you at the end of the alphabet, this is a little bit like when everyone is clearing out of the line ahead of you in the [03:59:18] airport queue or somewhere else where you're waiting in a line. Yasmeen Long?

Okay. Richard Lucarelli, L-U-C-A-R-E-L-L-I, Richard Lucarelli. We'll go to the next. Sharonann Lynch, [03:59:48] Sharonann Lynch. Zak Martinez, Zak Martinez. We'll move. Estela Mata, M-A-T-A, Estela Mata. [04:00:18] We'll continue to move through. Linda McKibben, Linda McKibben. All right. Francesco Nocera, Francesco Nocera. [04:00:48] I see our process improvement here, that we'll be implementing, which is asking for confirmation when folks have joined the meeting and want to continue to provide public comment. Ramakrishna Pidaparti, last name P-I-D-A-P-A-R-T-I, Ramakrishna Pidaparti. [04:01:18] We'll continue to move forward. Tumma Rama Rao, R-A-M-A-R-A-O. Cyrus Rangan, last name R- A-N-G-A-N, Cyrus Rangan. Elizabeth Reego, last name R-E-E-G-O, Elizabeth [04:01:48] Reego. Next, Beatrice Setnik. Beatrice, I see you're ready to go.

Beatrice Setnik: Oh, good afternoon. Yes, can you hear me? Yeah. Thank you for taking my comment. My comment is around the acquired immune immunity through COVID infection and the need for ongoing studies. Given the large Tel-Aviv study that has [04:02:18] given promising results on natural acquired immunity through COVID infection, this really needs to be also evaluated with some standards for individuals who have gotten acquired immunity and in light of the vaccinations and the mandates providing options that are scientifically data-driven as this is a large concern, especially for individuals who are otherwise healthy, who may have acquired immune response [04:02:48] and may otherwise be having to take vaccines, which could impose adverse events. So some of the important lessons from pandemics such as this is really to carefully also evaluate innate immunity, as well as other viable treatment options, as well as other sources of medications that are both, whether they're currently approved or in development, but the consistency also [04:03:18] of safety data and the foundations of vars and improving structural post-marketing data, so that information is more transparent, is very important going forward in these types of scenarios so that we have reliable data-

Susan C. Winckler: 10 seconds.

Beatrice Setnik: ... post-marketing data to rely on. Thank you.

Susan C. Winckler: Thanks so much, speaker Setnik. Our next registered speaker, Rensi [04:03:48] Sutaria, Rensi Sutaria. Getting to the last two pre-registrants, as a reminder,

participating in the public comment period does require registration in advance to give us this list. And so we have two final registrants, and then we will be turning it back to [04:04:18] Dr. Bugin for the last portion of the meeting. So Cindy Thompson, Cindy Thompson, T-H-O-M-P-S-O-N. All right, and then our final registered public comment provider, Lucy Vereshchagina. Lucy, please go ahead.

Lucy Vereshchagina: [04:04:48] Thank you, Susan. I'm Lucy Vereshchagina, the vice president of Science and Regulatory Advocacy of the Pharmaceutical Research and Manufacturers of America, and I'm speaking on behalf of pharma today. First, I would like to say thank you and congratulations to all the speakers and panelists today. Great discussions and a great meeting. Also, I would like to express our appreciation for the efforts that their day has taken in responding to the COVID pandemic [04:05:18] while continuing to perform mission critical work in those demanding time. And as heard many times today, [inaudible 04:05:26] by pharmaceutical industry are utilizing novel approaches to clinical trials, facility inspections, manufacturing supply chain to support continued innovation and inform timely regulatory decision-making. Thanks to this continued innovation by pharmaceutical companies who are able to deliver safe and effective COVID-19 vaccines and treatments to [04:05:48] patients in record time. This swift response to COVID-19 is a testament to effective and efficient collaboration with an industry [inaudible 04:06:02], federal agencies and other third parties. Sustaining an ongoing collaboration between the public and private sectors is essential to ensuring the safety and continuity of the supply chain and pandemic preparedness, and it's also important for [04:06:18] industry's ability to advance and manufacture existing and future innovative medicines.

Susan C. Winckler: Thank you so much, speaker Vereshchagina. We've hit that dynamic where we allocated time based on the number of folks who registered and needed to stick with that time commitment, but really appreciate all of the comments that were made. I'll note as well, there [04:06:48] is a docket open for this meeting, and so we encourage folks to submit comments to that docket, and then they will all be captured in this together. So, thank you for those who signed up to provide public comment and did so. The docket is open until December 28th, so a significant amount of time to provide that comment. I'm now going to pass the microphone back to my colleague, [04:07:18] Kevin Bugin. There may be a bit of a delay as we do that, so know that, in fact, Kevin is returning to the microphone and will close us out for the meeting. So I'll count you down, Kevin, please pick up and take us to the final session.

Closing Plenary

Kevin Bugin, PhD
*U.S. Food and Drug Administration &
former Federal COVID-19 Response or Countermeasures Acceleration Groups*

Kevin Bugin:

All right. Hi everyone. So I think we still, by my account, have little over 200 people still on. So I want to thank you all for this incredible marathon session of a lessons learned, which [04:07:48] honestly, we owe nothing less than that, given the marathon of a pandemic or public health emergency that we're in. I recognize again, it's been a long day. I've been standing the entire time, it was that captivating. I'm going to go ahead and quickly go through some takeaways and get you all out of here early, so you can move on and get to drinks or get to dinner. Firstly, a couple of takeaways from our two opening keynotes. I think the main for me [04:08:18] were that it's important to take the time to take stock, even though we're still in the pandemic.

That's because we've made substantial progress since the beginning of this pandemic. There were solutions that we've implemented already, solutions we may still be trying to implement and we're learning as we go now and then solutions that we simply need to continue to work on and make sure we do implement for the next pandemic. The common theme I heard throughout the day was, "You can't implement many of these things in the midst of a pandemic. It's something that [04:08:48] you have to have there already." Initial clinical research efforts, for therapeutics at least, were very scattershot and this created a lot of barriers to generating actual evidence, early on at least. It's tough when you have a system that's overburdened by cases, which we heard about already multiple times today, when you also have to deal with competition with those trials, that maybe are not going to lead to evidence that we needed to evolve the standard of care.

There was a remarkable collaboration, [04:09:18] whether that be what was described with the active program between NIH, FDA, HHS, and CDC, the academia institutions and industry, or the extraordinary all-of-government collaboration that we saw in response to COVID-19. This was certainly also something that we carried forward into this collaborative lessons learned effort, and, I would like to thank again, all those participants who joined us today and stuck with it through all the panel sessions. You are also our partners. You're our collaborators in this process of learning about [04:09:48] these lessons learned and how we can move them forward. Lastly, the President's American Pandemic Preparedness Plan, which was released earlier this month, lays out a very, as Dr. Collins mentioned, resource intensive, but ambitious plan for how to be prepared for future pandemics, and we saw a lot of alignment or commonalities with some of the lessons learned and themes from today, so hopefully that will give us some additional assistance or support as we try to make progress moving forward.

[04:10:18] Moving into the first panel on research scoping and prioritization, I heard in a public health emergency, there's this strong desire to help patients, and this was clearly seen with everyone jumping in, all hands on deck, trying to help, but not knowing how they should help. So, having a preparedness plan that can communicate what can be done from day one... Something I love to quote, I can't remember the person who said this, who I should attribute it to, was that from day one, need [04:10:48] to randomize that first patient. We

need to know how we can get that information and that guidance out so that we can work in the most coordinated and efficient way as possible. Now, when determining criteria for scoping and prioritization, I heard the need to consider scientific considerations, such as the mechanisms of actions of the drugs, the type of safety databases we need, but we also need to think about scalability and the available clinical supply, not just for the research, but of course, for getting it out to patients who will need it and manufacturing as well.

While there [04:11:18] are immediate term goals, we need to also keep the long-term pipeline and the broader view in mind. There's going to be that valley of death that we need to bridge and that's an important intermediate goal as well. How do we get from those phase one trials into the phase two and three and beyond. We need to make sure our trials are designed to yield actual evidence. They need to be adequately powered. They need to have the right controls, etc. We need systematic communication channels to promote timely information sharing. You can have a great plan, but [04:11:48] if nobody knows what it is, it's not going to do you much good. We need strong and continuous investment in pandemic preparedness, including infrastructure at the community and therapeutic areas such as in the antiviral R&D program that we've heard about.

I'll jump right into the next panel, which was on infrastructure and resourcing. Clearly there are networks and infrastructure currently, and were at the beginning of the pandemic, but they exist in different states of readiness, was the note that I made. Interoperability, rapid [04:12:18] coordination of new and larger networks, really necessitates that was required was difficult in real time. The key question, I think I mentioned this earlier, is how do we keep that needed infrastructure warm and ready? I'll come back to that question because I thought I also heard a really great answer to it as well.

Now, also keep in mind, what I heard from this panel discussion was the underlying infrastructure and resource circumstances were changing on a regular basis. We certainly saw this from the U.S. [04:12:48] Government's response in the operation, but certainly we heard this from our panel discussion as well. There were shifts and, of course, more needed remote and decentralized trial practices that use some digital health tools, but it was a struggle to implement those, not for lack of trying or for lack of flexibilities. We heard that there was great collaboration between industry and academic partners and regulators on how to implement those tools, but they were new. Anytime you were trying to implement something new, that can be challenging as you [04:13:18] build that self-efficacy with those tools. Then, of course. I called them basic needs, but the panel described fundamental lacking PPE, personal protective equipment, and, of course, the clinical research professionals that we would need to conduct clinical research.

Lastly, this pandemic has taught us the role of emerging variants and the evolution of standard of care over time really does make this a very challenging situation to manage, within the infrastructure and resources that we have. Also,

[04:13:48] a key point and it deserved its own bullet, at least in my mind, and it goes back to what I thought was the answer to that first question about how you keep the needed infrastructure warm and ready was, we didn't have infrastructure that actually could reach out to where those patients were, those underserved and underrepresented patients who unfortunately were disproportionately impacted by this pandemic. We really need to engage with those community sites more and bring them into the networks. Identifying and addressing their needs may be the answer to that key question.

Kevin Bugin:

[04:14:18] Moving on to panel three and I had to split this one into two slides because that was such a rich conversation and it was just difficult to stop capturing important takeaways. I'll begin by, the way Sarah and Mark had described this, was the importance of right sizing the research question, and then matching that up to the capacity that you'll have at the sites from the get go.

And I think inherent in that is, is thinking about that capacity at new sites and new networks and how do you get that up to a new level of normal, so that you'll have the necessary [04:14:48] capacity to answer the right types of questions that you're going to be needing to respond to in a pandemic or a public health emergency. This will require engagement at community trial sites. I took some great takeaways from Dr. Cooper as remarks as well. We need to think about those social determinants of health. Will you have the basic access to high quality healthcare? If you can't reach an academic medical center, then that's not going to be a medical center that can reach those patients. [04:15:18] Then of course, we need to think about eligibility criteria and its impact on diversity. I think a lot of times we think about eligibility criteria on getting to the heart of our questions around efficacy or around safety, but we also need to think about its impact on diversity and the types of patients that are underrepresented in our trials.

Next, the research needs to be as simplified, standardized, and as well-supported as much as possible, and really thinking also about how that question or that should be addressed internationally as well. I bucketed [04:15:48] in things such as the regulatory requirements for central or single IRBs, the administrative requirements and legal requirements as well, such as indemnification being much more clear and well understood for research entities during a pandemic, especially. Then, of course, addressing the overhead or the management challenges such as managing payroll and managing the risk of taking on clinical trials, contracting and other agreements, which really can bog down things in standing up a new trial. We saw amazing mountains being [04:16:18] moved during this pandemic, with some of the contracting and other agreements for some of the active trials being pulled off in a month's time. This is something that... Even a month seemed way too long when you're dealing with a pandemic and you really want to try and get patients enrolled as quickly as possible.

Of course, also thinking about how to expand the investigational drug and pharmacy management components. These two bullets here, particularly, I heard a comment from Dr. Brown, I believe, was about how do we modularize this? You might think about those right sized questions to the right size [04:16:48] capacity, to the right tools that simplify and standardize this, so you can almost pick and match and line up what those different modules might be. As far as the additional takeaways, another great quote, I'm sorry, Dr. Brown, but you were really on today, what do clinicians and healthcare providers do? Do they treat or do they respect, treat and learn? I think that's a key takeaway and the rest of the slide is really channeling or leading off of that. Thinking about training the next generation as an opportunity to [04:17:18] really accelerate the needed culture change for those next generations of clinical care providers or clinical researchers, and really, they're one and the same.

Really integrating all the novel tools and technology, all the novel clinical research, that we might be doing into clinical care and this needs to be as widely available as possible. With regards to that culture change, that's obviously needed and I took a couple of notes about what we need. Although this is probably not exhaustive, but we need true stories that are really compelling. They demonstrate [04:17:48] a real value proposition for communities, which as we've been talking about all today, I think engaging those communities and making sure they're in the mix for the infrastructure, they're part of the clinical trial, so that we execute, is critical. And of course, adjustments to all the broader ecosystem, the frameworks that we use to come up with research questions, the types of designs for studies, the incentives that we have all to enable research in clinical care, and lastly relationships that will reinforce that change over time. That could be relationships at the institution [04:18:18] or hospital level. It could be relationships with academia or broader research entities such as the NIH or with industry or with the FDA and so on.

So hopefully that was the speed round version of all the takeaways. We will get these updated slides posted onto the Reagan-Udall Foundation website here, probably in the next coming day or so, as well as the recording. As I mentioned earlier today, there will be a summary that will build on the pre-read that is currently on the Reagan-Udall Foundation. If you haven't already read it, I highly encourage you [04:18:48] to do so. We'll try to fold in these takeaways and some of the additional comments. We'll give our panels an opportunity to weigh in and add anything additional there, as well as some of the public comments that we heard, as best we can. Lastly, I think Susan mentioned this, the docket is open and feel free to send in those comments. I believe it's going to be open through the end of the year. Once that closes, we'll be summarizing all of that feedback and there will be a supplement to this additional summary report that I mentioned today.

Lastly, but not least, again, this is a very long journey. [04:19:18] We're trying to make changes that I think folks have been talking about in the clinical research space for years, if not decades. I think we have a lot of convergence now and it'll take everyone who's here today, or was here today, to help us move forward.

We want to thank you all for being here and helping us drive change and really make a difference so that we can be prepared, not only for pandemics in the future or other public health emergencies, but just to do the best clinical research possible and bring that into the clinical care setting. So with that, I will [04:19:48] close us out. Again, thank you all for participating and thank you to all our panels and for the organizers from Reagan-Udall Foundation for the FDA. Thank you very much and have a great night.

PART 4 OF 4 ENDS [04:20:14]

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