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Monoclonals and More: Issues and Opportunities with Early COVID-19 Treatment Options
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Shayne Brannman: Greetings. On behalf of the US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, I'd like to welcome you to ASPR's Technical Resources Assistance Center and Information Exchange webinar titled Monoclonal and More: Issues and Opportunities with Early COVID-19 Treatment Options. Before we begin, we have a few housekeeping items to note. The webinar is being recorded. To ensure a clear recording, everyone has been muted, however, we encourage you to ask questions throughout the webinar. If you have a question, please type it into the question section of the GoToWebinar console. During the question and answer portion of the webinar, we will ask the questions we received through the console. Questions we are unable to answer due to time constraints will be followed up directly via email after the webinar. To help you see the presentation better, you can minimize the GoToWebinar console by clicking on the orange arrow. Today's PowerPoint presentations and speaker bios are provided in the handout section of the GoToWebinar console, and will be posted along with the recording of this webinar no later than Monday 15 November on ASPR TRACIE. Next slide.

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My name is Shayne Brannman, I'm the director of ASPR TRACIE and I want to welcome new and old friends to this webinar. I want to thank you for what you do daily to enhance the preparedness, response and recovery activities of your healthcare entities and communities. Your role is so vital to addressing the daily and arduous challenges being presented. So your willingness to spend your time with us today to further advance your knowledge is noteworthy. I also want to convey my heartfelt thanks to our awesome lineup of panelists and moderator for this webinar. Your willingness to lend your precious time and share your substantive expertise to others might benefit is commendable and genuinely appreciated. And lastly, thanks to Audrey Mazurek and the ICF TRACIE crew for coordinating this webinar for our new friends to ask for TRACIE on the webinar today. This slide depicts the three domains of ASPR TRACIE, Technical Resources, Assistance Center and Information Exchange. If you cannot find the virtual resources you're looking for on ASPR TRACIE website, simply email call or complete an online form and we'll respond to your inquiry in a very time, fashionable way. Next slide.

This slide depicts some of the virtual resources that are available to you on this topic. So please check them out and return off and as new resources are continually being added or updated. Next slide.

So let's get to this. I will now turn it over to Dr. John Hick from Hennepin Health, who also serves as the Senior Editor for ASPR TRACIE, who will serve as the moderator for today's webinar. John, let's start this important discussion today. Thank you, sir.

Dr. John Hick: Shayne, thanks so much for all you do. And thanks to everyone for taking the time to join us today. I know that many of you are burdened right now by significant numbers of COVID patients by vaccination challenges by many other challenges. So we hope to make this useful presentation today. It's really important when we talk about both monoclonal as well as other therapeutics that there's intense collaboration between the clinicians, state and local public health and the federal government. The feds are at this point in charge of allocation of many of these resources, you know, using a mechanism to make sure that there's equitable access in relation to the incidence of disease within the state. After that, though, it really is up to the state public health departments and the health care systems and clinicians to figure out how to best use these resources. Using some guidance from NIH and IDSA that we'll hear about, there is some framework for deciding, you know, who should have access to which particular therapeutics in what fashion and what venues. But there is quite a bit of planning that needs to be done in anticipation of some of these agents who have to come as well as, you know, continuing challenges with administration and availability of monoclonal antibody. So we're looking forward to a great discussion today. And we'll get right into our next speaker, who's Dr. Dan Hanfling. He's the Co-Chair for the Forum on Medical and Public Health Preparedness for disasters and emergencies at the National Academy of Medicine, and as a crisis centers of care master from way back. So, Dan, thanks for joining us today to set the stage a little bit for, you know, allocation of scarce resources such as these therapeutics.

Dr. Dan Hanfling: Well, thanks very much, John, and thanks to all of the panelists and the TRACIE team for the opportunity to collaborate on this important discussion. And as noted, along with you, John, you know, I've helped to lead some of the planning and discussion over the past decade plus on the issue of scarce resource allocation. And that is the topic that I want to introduce on this webinar as a level setter for the discussions that will follow. Next slide, please, or this slide.

Perfect. So how do we decide who gets access when there are therapeutics and limited supply? And for those of you who are familiar with the crisis standards of care framework, this will be a quick review. For those of you who may be less familiar, let me draw your attention to the fact that over a decade ago in 2009, during the H1N1 influenza outbreak, it was the great concern of the leader of ASPR at that time, Dr. Nikki Laurie, that this might be the big crisis that we were fearing. And so the National Academy of Medicine was asked to convene at that time, the Institute of Medicine asked to convene an ad hoc committee to address the four following questions, who should receive care when not all can be treated? How should limited resources be applied to managing the requirements of a catastrophic event when the health system will be unable to care for all? How should clinicians make decisions related to the delivery of medical care? And should the standard of care change when health care has to be delivered under catastrophic conditions?

And so the committee convened and in short order developed both a definition for what we call crisis standards of care and a framework. The definition, in simple terms, describes a substantial change in usual healthcare operations, and the level of care possible to deliver that is made necessary by a pervasive or catastrophic disaster. And it is quite clear that COVID has met all of the criteria of this definition. And so crisis standards of care, as we have learned throughout the course of the last 18 months, had been on the forefront of a lot of plans. And in fact, unfortunately, policy decisions that had to be invoked, most recently in Idaho, Montana, the state of Alaska, and now over the last few days, the state of Colorado, and shortly before that, New Mexico. So crisis standards of care as a framework is understood as a means by which to make some of these scarce resource allocation decisions. And the bottom line in the framework is that it is governed by both the rule of law and ethical considerations that are really the foundation for these decisions as we go forward. And I believe that we'll have a chance to get into that in more detail. Now, the truth is, is that with regards to pharmaceuticals as a scarce resource, we've been down this road before, particularly with regards to emergency medications, especially those that are available in the pre hospital environment, and oncology medications. And, in fact, along with John and other members of the National Academy's Crisis Standards of Care Committee, we participated with the Association for State and Territorial Health Officials, all the way back in 2012, to help them think through how we might adopt some of the National Academy principles for coping with and mitigating the effects of shortages of emergency medications. And that was a report that came out in 2012. And without getting into the details, we focused significantly on the importance of conservation, substitution and adaptation. And I would say that, in the context going forward for today's discussion, adaptation will be critically important as we think about flexibility needed to deliver on monoclonals and other antivirals in a scarce resource setting. Now, as I noted, the framework for crisis standards of care has really focused on ethical considerations. And you know, without getting into a full discourse on medical ethics, there were a couple of key areas that we have really highlighted. Accountability, that's accountability, both of the government to its subject if you will, as well as reciprocity, the fact that the population itself has some responsibility for trying to do the right thing to protect themselves and to protect their community. There's a duty to plan and after all, most of us who are participating in today's session are planners and it's our responsibility to think about how to bring together all of the various threads to make as comprehensive and as useful a plan as possible. And then there's the duty to treat. As clinicians, we are obligated, you know, we take an oath to deliver care and that is critically important. And so our goal is to balance both medical benefit and equity as we look at scarce resource decision making. This is not easy, as we all know. Next slide, please.

So who gets access. In January of this year, the National Academy of Medicine Standing Committee on emerging infectious diseases and the COVID-19 response, which is a group separate from the group that delivered the crisis standards of care work to the National Academies, actually was convened to look at the issue of monoclonal antibody allocation, and declared in a report that is available to you on the web, that the goal of equitable allocation is not to get every eligible patient to accept monoclonal therapy, but to identify the right patients at the right time. And they really highlighted the importance of transparency and fairness in making these decisions. And, indeed, linking both the January report to the work that had been convened over the last decade on the development of a crisis standards of care framework, the notion of falling back on a utilitarian

framework, I think has, by far and away become the overwhelming and consistently agree to approach for delivering on scarce resource allocations. The utilitarian framework essentially states that patients who have the greatest risk of hospitalization and death should be given access to those lifesaving medications. In other words, we're trying to do the best for the most given the resources that we have available to us. Now with that in mind, you know, what we have highlighted within this utilitarian framework is the importance of being able to identify impacted population. So being able to realize and anticipate proactively who's at greatest risk by doing so targeting those areas and those patient populations with the highest incidence of disease in the community. And in the context of trying to do the best with what we have available to us, prioritizing treatment over prophylaxis. Now we're going to get into this in a little bit more detail. I'm quite certain as we go through in the presentation on both the monoclonal and other antivirals as well as in the discussion. But I do want to caveat the notion of treatment over prophylaxis because yes, in a perfect situation, if we had availability of resources for all, the immunocompromised would be a top priority for receiving protective countermeasures. That would include pre exposure or post exposure prophylaxis. But this becomes an issue of scale if we think about the number of Americans who fall under the category of immune compromised the National Institute of Environmental Health estimates 24 million Americans have an autoimmune disease, there are about 2 million new cancer diagnosis in the United States each year, there are those with diabetes patients over 80 years old smokers etc. The list goes on and the numbers increase significantly. So under conventional standards of care by which we define the ability to deliver medical services per conventional or usual standards, and we're not encumbered by emergency conditions, there's no question all those who are at risk would receive the medicines that would protect them. But under crisis standards, in which we're forced to make these very difficult allocation decisions, this is where the utilitarian framework really has to be emphasized. And if we only have enough countermeasures to treat, and not enough to prophylaxis, then we have to prioritize treatment and emphasize the importance of protective measures and very close medical monitoring. So that treatment can be started for very first signs of a change in clinical status. So that is a caveat. Now, I'll conclude this opening sort of level setting discussion, if you will, around the importance of equity and I think COVID made very clear to all of us just how much work we have to do with regards to issues of systemic racism and other structural impediments to the delivery of care, and we have to recognize and support the disadvantaged. Now that being said, you know, there has been a lot of work a lot of excellent work done looking at indices such as the, you know, ADI and the social vulnerability index, the area deprivation index and social vulnerability index, as means to appropriate resources where they are needed. You know, it's my sense that these are very, very useful tools for planning, not necessarily for response. And that too can be an issue for further discussion. But there's no question at the end of the day that the equity lens is really important as we look at how to make these very difficult decisions around who gets access to scarce limited supply of therapeutics. So with that, John, I will stop and turn it back to you. Thank you.

Dr. John Hick: Thanks so much, Dan. It's interesting, as we look at, you know, SBI versus ADI, the ADI actually identify as a lot of rural and frontier areas as being very disadvantaged. And I think that certainly comes into play when we talk about administration of, you know, monoclonals are available, availability of some of these therapeutics that we'll talk about a little later in the webinar. So thank you for that. Next slide, please.

So I just like to introduce our Rajesh Gandhi from Massachusetts General Hospital, who's an infectious disease physician there. He is also a panel member of both the National Institutes of Health and Infectious Disease Society of America's Treatment Guidelines Panels, although he's speaking today about his individual opinions. So, Rajesh, thanks so much for joining us and outlining some of the exciting, you know, opportunities and outcomes of these therapeutics.

Dr. Rajesh Gandhi: Sure, it's a real pleasure to be here with you all. And I'm looking forward to the discussion. I've been asked to really review some of the evidence that has gone into the recommendations around in particular monoclonal antibodies, but also to point out some new interventions that are currently on the horizon and that may be here soon. And again, I'll reiterate that I'm speaking on my own behalf and not on behalf of the NIH COVID-19 Treatment Guidelines Panel nor under behalf of the IDSA Treatment Guidelines Panel. So let's go ahead to the next slide, please.

So the evidence I'm going to be reviewing really falls into this treatment spectrum. We know that SARS-CoV-2 infection starts out asymptomatic when people have a positive test but no symptoms. They can then develop mild symptoms such as fever, cough, taste, smell changes, but no shortness of breath. Moderate illness is typically defined as having a preserved oxygen saturation, but evidence of lower respiratory tract disease. Severe illnesses, one people end up typically in the hospital with an oxygen saturation below 94% to keep near and extensive lung infiltrates, and then of course, critical illness, as well there's respiratory failure, shock, multiorgan dysfunction or failure. And the reason I put this up is because we think that the disease pathogenesis, which is where the treatments come in, is driven early by viral replication, viral loads in the nasal pharynx peak just before people get ill, and then tends to taper off in the nasal pharynx as people get into moderate and severe illness versus inflammation, which we won't be talking during this session about anti inflammatories. But inflammation is most prominent when people have severe disease, which is why anti inflammatories are typically used in hospitalized patients. So we're going to focus on antivirals, and we're going to focus on antibody therapy to begin with, because this is what we use in the outpatient domain. Next slide.

So here are the three authorized anti-SARS-CoV-2 monoclonal antibodies. Just as a reminder, these are antibodies that target the spike protein of the SARS-CoV-2 virus. These are a compilation of data from phase three placebo controlled clinical trials, these trials were all done in non-hospitalized patients with mild or moderate COVID-19. And were done in individuals who had at least one risk factor for severe COVID. And the reason for that is, in order to see an effect, you need to have a higher risk population. Because low risk populations with no risk factors tend to have a lower by definition, lower progression rate to severe COVID. So these trials and the numbers that you're seeing on this screen have 70 to 85% reduction in hospitalization and death with each of these three antibodies or antibody combinations were done in high risk populations. And as you know, the FDA has authorized these three products. Next slide.

A little bit more granularity around the authorization. This is for individuals who are not hospitalized to have mild to moderate COVID-19 are at high risk progression. And this is important are within 10 days of symptom onset. Now those trials that lead to the clinical trials data, often people were treated even much earlier than 10 days they were often treated within three or four

days of symptom onset. But nevertheless, authorization gives a little bit more of a buffer. This is a reminder for me to say that testing and treatment really are hand in glove you need to be able to test quickly and get a result quickly so that you can treat quickly. Next slide.

Now a bit of a detour for a second I'm going to say a word about anti-SARS-CoV-2 antibodies for prevention before we come back to treatment with small molecules. So let's go to the next slide.

So here are the authorizations for post exposure prophylaxis, casirivimab and imdevimab either given subcutaneously or intravenously, or bamlanivimab/etesevimab given intravenously, both are authorized for post exposure prophylaxis, and individuals who are at high risk for progression to severe COVID-19 that same hallmark as for the treatment trials, but also here they add and are not fully vaccinated are not expected to mount an adequate immune response to COVID vaccination for example, immunosuppressed individuals, and then this is conjoined with an exposure within six feet for more than 15 minutes in the same household, direct contact, exposed to respiratory droplets as an example or someone who's at high risk of exposure because of them, for example, being in an institutional setting such as a nursing home or prison. Let's go to the next slide.

I want to say a word about something that the FDA is currently reviewing, which is the use of a combination monoclonal antibody product for pre-exposure prophylaxis. So these are data that were presented at IDWeek this year from the PROVENT study. This is a study of intramuscular delivery of tixagevimab, cilgivimab, which is a long acting antibody, cocktail versus placebo. The people who are in this trial about 6000 or so were adults, they had negative testing and for SARS-CoV-2 and this is quite important, they were unvaccinated. This trial and the results that come from this trial are in an unvaccinated population. They were randomized two to one to either get the long acting antibody cocktail given intramuscularly or placebo. Who was in PROVENT? About 5000 or so ultimately were included. Over age 60 was about 43%, obesity was present and about 42%. You see some other risk factors for severe COVID such as cardiovascular disease COPD. The bottom bullet, though, in the box I want to highlight, only 3.8% of people in PROVENT were immunosuppressed. What were the results? There was a 77% reduction in symptomatic COVID-19. You see the two curves diverging there, the prophylaxis curve is the antibodies, the grayish curve is placebo. And that's that 77% reduction. Next slide.

Just a couple of slides on what is on the horizon, and we'll see where this goes. But we'll start with a small molecule antivirals for SARS-CoV-2. So now we're shifting from antibodies to small molecules and these are the drugs we're going to talk about now are oral not potentially administered. So we'll start with molnupiravir. This is an oral inhibitor of SARS-CoV-2 replication. It works by inducing mutations in the virus a mechanism called viral error catastrophe. The data and these are data from a press release not from a peer reviewed publication nor even from a press nor even from a preprint. But in the phase three move out study non-hospitalized adults, mild to moderate COVID-19. One or more risk factor for severe disease, symptom onset within five days of study randomization. So again, they got in there quickly randomized the molnupiravir at the dose shown here 800 milligrams twice a day or placebo for five days. The way this is given is four 200 milligram pills given twice a day. And then results I'm about to show you are on an interim analysis of just over 770 individuals. Next slide.

Here are the results. And before we get to the results, the median age of the trial participants were in the mid-40s 14%. Again, in this trial also were over the age of 60, obesity was by far the most common risk factor 77% and diabetes in 14%. This was an international trial. And the majority of participants, I believe came from outside of the US. You see the results on your right hand side in the table the rate of hospitalization and death with molnupiravir was 7.3% as compared to placebo 14%. Zero deaths in the molnupiravir group eight in the placebo group representing a 48% reduction in hospitalization or death. A subset of individuals had testing for gamma delta and new variants and the drug seem to be active against those variants. The UK has authorized this sometime last week. In the UK authorization materials, they comment that there's no dose adjustments for renal or hepatic impairment and no anticipated or identified drug interactions that's coming from the UK material. The US FDA has convened an advisory meeting at the end of this month to consider the evidence as well provide guidance around this drug. Let's go to the next slide.

And then the other small molecule that certainly has been in the news goes by the letters that you see there, I'll call it 332 for short. This is an oral SARS-CoV-2 protease inhibitor. It is given with a drug that those of us who do HIV work are familiar with called ritonavir. The ritonavir is an anti HIV drug, but here it's being used as a pharmacological booster. The data that's been released through a press release is shown here. It's a phase 2/3 trial called EPIC. It was done in high risk non-hospitalized patients randomized to get the 332 drug with ritonavir. That's a total of three pills every 12 hours or placebo for five days. Here two is an interim analysis of patients treated within three days of symptom onset. So really quick, 774 individuals, you see the results in the table, the rate of hospitalization and death was 0.8% in the drug group with zero deaths. In the placebo group, it was 7%, but seven deaths, looking at hospitalization and death, that's an 89% reduction. There were similar reductions in hospitalization or death among people treated within five days of symptom onset. So a little bit more of a buffer there. That's about 1200 people. These are the results for high risk patients, we're told that it's also being evaluated in lower risk patients and for post exposure prophylaxis with those trials not yet completed. Let's go to the last I think, pause to the last slide here. One reminder, currently the NIH guidelines and the CDC recommend that for people who develop COVID-19 After receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions including use of and timing of treatment with monoclonal antibodies, that is breakthrough infections, if people will otherwise meet criteria should be considered similar to non-breakthrough infections in terms of monoclonal antibodies. Next slide.

So here's kind of a summation of what we've been talking about in terms of that treatment spectrum. Pre exposure prophylaxis I put in all caps vaccine, vaccine is really the way to prevent SARS-CoV-2 infection. I put a question mark next to the cocktail that's being evaluated by the FDA. We talked briefly about post exposure prophylaxis, this is in the exposure category. Once people have mild to moderate illness, we've talked about the three antibody products for high risk patients, I put a question mark next to malnupiravir and I'll put a question mark next to the 332 drug, which I'm sure will also be reviewed by the FDA in the future. And then once people are hospitalized, we're talking about other interventions, not the focus of today's conversation. So let's see the next slide.

Yes, that's it for now. And again, thank you for having me on the panel.

Dr. John Hick: Great. Thanks so much, Raj. How do other companies just sit around and come up with names that are almost impossible to pronounce? Do you think we'll be seeing additional combinations of existing antivirals like ritonavir and other, you know, protease inhibitors and things in combination with other antivirals? Is this something that you think these cocktails could be, you know, a wave of the future?

Dr. Rajesh Gandhi: You know the issue of combinations is a good one. I think, certainly, for chronic viral infections, you absolutely need a combination. So for hepatitis C, as well as for HIV monotherapy really doesn't do the trick. This may be a little bit more analogous to influenza, where the duration in an immunocompetent person a viral replication is pretty short on the order of maybe seven days or so. And so it may be that a monotherapy with either, let's say, malnupiravir, let's say the 332 drug, or even a monoclonal antibody may be quite unlikely to lead to resistance. I haven't personally seen resistance data from the oral drugs, I don't think those data are yet available. So this may end up being a bit more like influenza, where for immunocompetent we use also baloxavir. For influenza, there are combination trials that are underway for influenza. I think where combinations are likely to be needed are in immunosuppressed individuals where viral replication can really go on for, you know, quite some time. We know out for several months. So in immunocompromised, I can see real value and studying a combination oral antivirals.

Dr. John Hick: Great. Thanks so much, Raj. Our next speaker is Jay Epstein with the COVID-19 Therapeutics Response arm of HHS/ASPR to talk a little bit about distribution and opportunities with these agents. Jay, thanks so much for taking time today.

Dr. Jay Epstein: Thank you very much, Dr. Hick. If I could have the next slide, please.

So I'm going to talk about the federal government role in the procurement and distribution of the monoclonal antibodies against SARS-CoV-2. So the fundamental concept is that the federal government has a responsibility for ensuring rapid and equitable access to medical countermeasures in a public health emergency. The strategies that the government employs may include the development of products, their procurement, their distribution, guidance on distribution and administration, feedback reporting. And this is especially true for novel products, as opposed to repurpose products. When the demand exceeds the supply, the government typically will invoke allocation strategies in order to allow equitable access and to ensure both a predictable and a consistent supply with broad applicability over geography and time, and also with the capability for the jurisdictions. That is to say the states, the territories and the Federal jurisdictions like Department of Defense or Indian Health Service, to target the delivery and the administration of products to meet the needs that are unique to their jurisdiction, for example, to best identify where the high risk populations are, and the areas of the highest disease burden, as well as logistical constraints. And as Dr. Hanfling said, there had been historic examples of government allocation in which included allocation of oseltamivir in the 2009 to 2010 H1N1 influenza pandemic, as well as the initial distribution of COVID-19 vaccines. The USG or government purchase and distribution of monoclonal antibodies for COVID-19 has played a major role in the COVID 19

pandemic response by providing the first and only therapy for early treatment of symptomatic infections to prevent hospitalizations and deaths. And this role is still evolving. Next slide, please.

So equity consistent with the crisis standard of care framework is a cornerstone of the federal approach to the distribution and administration of medical countermeasures. The federal government believes that when supplies are critically limited, jurisdictional partners are best positioned to determine how to ensure access to these products for their populations. So on that basis, the government has been allocating monoclonal antibodies to jurisdictions based on their relative need. Again, the concept is that the jurisdictions rather than the government, best understands the need in those areas, and also, as has been mentioned, can use advanced tools such as the CDC social vulnerability index, the area, deprivation index, and geospatial mapping of provider locations to address equities through the prioritization of the ordering sites, as well as determining the allotments to those sites. Next slide, please.

So the story with respect to the monoclonal antibodies starts in November 2020, when FDA first gave emergency use authorizations. And it was at that time that the Office of the Assistant Secretary for Preparedness and Response began allocating monoclonal antibodies to jurisdictions. I should mention and it's important that the NIH ethics group was consulted on the strategy for equitable allocation of a limited supply. However, as supplies became available relative to demand, unrestricted ordering was put in place starting in February of 2021. And over time, on the order of 7000 individual sites submitted orders. However, this all changed with the surge of the delta variant that began in July and became dramatic in August, we had a phenomenal increase in orders, roughly from 10,000 doses per week to over 220,000 doses per week, which threatened to exhaust the available supplies of monoclonal antibodies within just a few weeks. Consequently, in September of 2021, the Assistant Secretary for Preparedness and Response reinstituted allocations, and at the same time began a massive procurement effort to ensure that there would be an ongoing supply and to make sure that it would be available equitably both geographically and temporally. So under this allocation systems, the jurisdictions receive a proportionate share of a weekly weighted average of newly reported diagnosed cases and hospitalizations. Next please.

So as Dr. Gandhi already said, we have an evolving landscape. This situation of the pandemic has been and continues to be dynamic. And as the landscape evolves, the Office of the Secretary for Preparedness and Response will continue to balance allocation of monoclonal antibodies in response to product availability and take into consideration also user preferences for products with different routes of administration and logistical complexity. As it has been said, monoclonal antibodies for pre exposure prophylaxis are under FDA review. And distribution of those products may warrant different strategies then for the early therapy in order to target the at risk populations as they may be indicated in an emergency use authorization. We don't know right now, how broadly or narrowly those intended uses will be defined. So again, the Office of the Assistant Secretary for Preparedness and Response anticipates a transition to commercial distribution of monoclonal antibodies through the healthcare system when crisis conditions resolve, and when monoclonal antibodies are no longer in limited supply. Equitable distribution strategies also will be needed for any authorized oral antivirals. But there the distribution sites will be selected in accordance with oral as opposed to subcutaneous or IV administration. And we don't know to what

extent the availability of oral antivirals will impact the demand for monoclonal antibodies, and also the supply because this could affect the production by the manufacturers. So in summary, the Department of Health and Human Services and the ASPR will continue to provide access to government purchase medical countermeasures for COVID-19. But challenges will persist to broad and equitable distribution with the prioritization of clinical use when products are in limited supply. But I think we need to understand that these are also new opportunities to advance the prevention and therapeutic response to COVID 19. So thank you very much. And back to Dr. Hick.

Dr. John Hick: Thanks, Jay. Grateful through your management to that process and avoiding sort of a first come first serve ordering system that tries to balance the needs in the States. And it gets a perfect transition to talk a little bit about the state level, and so on to Anne Zink, the Chief Medical Officer for Alaska Department of Health and Social Services, and I'm glad that at least cases are declining up there. But you all have been in a lot of ways uniquely challenged with this pandemic. Thanks for taking the time to join us.

Dr. Anne Zink: Yeah, great. Thank you so much, John. It's an honor to be here. And thank you to the other panelists, I always learned from you all, and it's really great to be able to spend this time to think about ways to move forward. I'm the Chief Medical Officer for the State of Alaska. I'm also the President-Elect for ASTHO, and appreciate just a few minutes to talk about the final mile. And some of the challenges at the state and local level and what this can look like.

Going on to the next slide, ASTHO represents the state and territories. And it's just impressively diverse. We live in a big, beautiful, messy democracy with a really complex healthcare system. And so thinking about how we interface health care, public health, and thinking about the overall mission is really dynamic, super interesting but very challenging. What may look like it really works well in Alaska may be very different in DC. And so want to make sure that I address kind of what it looks like here, but also across other states as well.

Moving on to the next slide, I think it's always helpful to speak a little bit in context. And so as I'm, you know, coming from Alaska, I'm just going to go over a few things in Alaska, because I think it highlights some of the huge challenges in the nation as a whole. I sometimes joke that Alaska is just a larger microcosm of what we see across much of rural America, it's just much larger here. And so you can see some of the gaps and strengths in a different way. So Alaska is bigger than Texas, Montana, and California combined. We have more coastline than the East Coast and West Coast combined. And 80% of our communities are not connected by the road system. So they're either connected by plane or by boat. And so that makes distribution and movement across the state incredibly challenging. We kind of have two structures that are overlaid on top of each other. I mean, there's a traditional healthcare system, but on the left, you can see our public health system. We have a very centralized public health system. So we don't have a lot of local public health authorities and many of them do a turret work, where they work remotely to support many of the regions you can kind of see the regions on there. But that's also layered in combination with the tribal health system 40% of the nation's tribes are here in the state of Alaska, we have 229 independent federally recognized sovereign tribes and nations, and working in coordination with them. All of their hospitals are 638 hospitals. And so they work quite independently from IHS. And in many of the regions, the tribal health system is the only health care system in that region.

And so being able to partner and work super closely with them is really important moving forward. We also have more veterans, per capita and more military per capita. And so thanks to all the veterans who have served as yesterday was Veterans Day, but these partnerships between state, local and federal really highlight when we have so many people in the state who have federal connections.

Moving on to the next slide, it's really great to think about how to ideally do this, but I am constantly reminded about how many people don't have access traditional health care systems. So in this Kaiser Family Foundation study, you know, 1/4 of adults, and nearly half of adults under 30, do not have a primary care doctor. And so when we're thinking about, you know, who would make sense for this medication, how are we going to get this out, this is where a lot of the work within the public health space has really had to focus, because they don't have a primary care doctor to talk to, or they don't have the time to be able to meet with someone. And so this is where we've seen pharmacies really stand in as well as many other partnerships moving forward. So when I'm thinking about these new therapeutics, this is what keeps me up at night, this group under 30, and how we're going to be able to connect the fact that they're not connected into the healthcare system with the overall treatment and testing. This is why we've had to stand up so much work at States to be able to respond, we've really seen is that industry and people's jobs play a gigantic role in this as well as other existing infrastructures, as mentioned, like the pharmacy structure.

So moving on to the next slide. These are just some partnerships that we've really had to implement and to be able to use in the state of Alaska, to be able to get out everything from vaccines to treatment options, talked about the pharmacies drive up and walk through clinics, we've actually had boot up clinics to be able to get out things like vaccines, as well as testing supplies for monoclonal antibodies. Many of our rural villages do not have a nurse practitioner or a PA, a physician, or a nurse, they have what are called community health aides. And so there's three different levels of community health aides, but they're kind of like community health workers, who live and work in those communities. And we built into their ability to give care, information about testing, but also monoclonal antibodies. So they've been doing a lot of subcutaneous monoclonal antibodies in these rural villages, but they don't really have the skills or expertise to do IV or IV infusion. So which monoclonal is available makes a really big difference for them, and making sure that we are giving them the skills and tools to be able to make decisions about the health care, which can be really challenging, given kind of the limited structure in that space. That's really then supported by these regional tribal clinics. As mentioned, schools clearly play a huge role. I sometimes joke that people don't know who the local public health leader is, and that's fantastic, but they know who their principal is, and they know who their teacher is. And so I think finding more ways to support the health of families via schools is going to be a key mechanism for distribution of information resources, as well as thinking about the public health experience. So things like offering antigen testing at schools, industry and workplace are invaluable in our seafood industry, with people who work on these ships for nine months of the year. So being able to provide them with treatment, if needed, such as monoclonal antibodies, we've delivered monoclonal antibodies on deep sea vessels working out in the Bering Sea and on cruise ships, because those patients aren't coming in. And we also don't want to transport a bunch of COVID positive patients, if we can safely keep them kind of in place and be able to treat them. So working with industry

and workplaces, I think is a huge area where I'd like to spend more time really diving into how we can support. Department of Corrections, another one, you know, having people come out of the correctional facility to access care can be really challenging in many ways. And so working with the Department of Corrections to offer treatment within the department, as well as early identification is critically important another area that we worked with. And then travel industry, we've tried to really use geography to our advantage in the state. But this can make some challenging opportunities. So we have testing at most of our airports. But if someone gets tested before they move out to a rural village, they test positive, how do you make sure that you connect where that person now is and being able to get them treatment options? So people move a lot, not just between places within Alaska, but between states. And really our systems are very located at a statewide or sometimes just a very local level and not a national level. And so this movement of people can be really challenging when you're trying to connect a test with a treatment option overall.

Moving on to the next slide, just a little bit more about the role of the state. You know, Alaska stood up a monoclonal antibody infusion center really early on, right, the very beginning of monoclonal antibodies, just because we didn't think that the private healthcare sector would be able to do this. And we were concerned about the lack of equity. If we were relying simply on the healthcare infrastructure, it would really bias those who really had access to health care and an effort to address some of the inequities we were already seeing in our data. Wanting to stand into that space is expensive, you know, setting up a place for people to get monoclonal infusion and staffing associated with it, but have now been working with additional contractors. Some of our EMS teams have been offering monoclonals at home. And that's been actually really useful. They've been able to test and educate the entire household, then if someone test positive and talk about household recovery, but really having to think about very different partnerships than just going to an infusion center. Again, cruise ships, being able to deliver a state has really had to stand in in distribution. So even instead of like Alaska, you know, having 20 doses of monoclonals is too much to center many of our areas. So both with vaccine as well as treatment, our state has had to really be a redistribution center really had to stand into the health care space, and be able to distribute one dose or five doses depending on what's needed. Particularly when we were incredibly short amount of monoclonals, and our cases were continuing to surge, it was just a day by day trying to move each space. The other thing is this, you know, that little asterisk on the bottom of your mail that says not in Alaska and Hawaii, and this goes through our territories, sometimes the normal delivery of mail and services and FedEx and these other systems that we use, don't go to all the places in the country. And so we've oftentimes had to stand in and be an intermediary shipping company on top of a distribution company to try to make sure that that final mile things are actually able to be distributed and get there.

Moving on to the next slide here, just some logistics that have been taking place. So again, movement between systems. So when one hospital needs it, moving it to another one working with the seafood companies, industry, again, like ConocoPhillips flights up to Alpine Medical Health and trying to get monoclonals up there when and you know way north in the Arctic Ocean. And our large crews that do a lot of oil work being able to get monoclonals out there. And a lot of work was sharing monoclonal so in particularly regions like Juneau having you know, if we have

monoclonals in one site, being able to share with kind of the local community around that area to be able to make sure each and every dose is used as quickly as possible and appropriately as possible.

Moving on to the next slide, something else I wanted to highlight was just it's hard to plan on changing demand. So here is Alaska's use of monoclonal antibodies. And you know, when we're at that, you know, bottom level, it's okay, we've got some space, we've got some capacity, and we can move things around. But what we really saw is that it's hard to set up systems that move as fast as this virus. This virus just moves so quickly and can cause outbreaks so fast, that it can be very challenging to then change the system or be able to move or be able to meet the demand of treatment options, or of other things such as testing moving forward. So here, you can see just the skyrocketing demand that we experienced here in the state with monoclonal antibodies.

Moving on to the next slide. Something that I think we really struggle with, and I think every state has struggled with this is that there are a finite number of people to respond to all of the same things. And so as cases client present positivity climbs, the testing then becomes delayed. A test that normally would take, you know, 12 hours to come back now is taking four days to come back. That's the same group of people who are then trying to offer treatment options. And so the entire system becomes incredibly bogged down. And we're just asking more of the same people over and over again. And so that idea of like, okay, we're going to test and then we're going to treat right away, works really great when the case numbers are low. But when those case numbers surge, the entire system kind of falls apart. And it becomes very challenging to do that. I have to say one thing that we really appreciated here in Alaska, I know other states have used this as well, FEMA set up these GSA contracts that we were able to then leverage to be able to get additional staff up into the state. And this helped to support not only our hospitals, but also places like our schools and our testing and treatment options. Because when we just surge all at once, we could not meet the demand for everything from testing to monoclonals to care within hospitals. And so being able to have those GSA contracts ready to go was incredibly helpful and something that we're hoping to spin down here shortly, but are continuing to use overall. So I don't want to forget about the personnel lift that these things take. And in the lift that's really happening within the public health workforce. We've seen a real loss of people within public health and the public health sector as this has become more politicized. But this takes a lot of personnel and people to think about the movement and how things move forward.

So moving on to next slide. These are some other challenges that we have been continuing to balance So it's really helpful to have the NIH guidelines on who to use monoclonals for having these kind of standardized approaches. But things that such as you know, high risk condition, were too vague for many of our healthcare providers to actually figure out how to interpret them. And there was also a lot of concern about liability when we did not have enough monoclonals to meet kind of the criteria under NIH. We have a Crisis Standards of Care Committee that meets once a week as well as meeting with our hospitals on a daily basis currently, to try to figure out allocation. And in that, we basically took the NIH guidelines and had to modify them to be able to make it more programmatically useful for the end user at the end to try to make sure it was a standard as possible across the state. So really had to define who was high risk, and then went through kind of

who were vaccinated and how we would recommend using monoclonals. So we basically said, anyone who's vaccinated 65 and older, pregnant, or those who met criteria for a three dose initial vaccine series. And so kind of taking those NH guidance, but having to add a bit more detail, a bit more meat on the bones to try to make it workable overall. There's just a lot of diverse authorities with a lot of diverse tools. Standing Orders, I think is another fascinating concept in here. You know, we're using public health to use standing orders through things like vaccination. But when it gets into treatment, particularly looking at the treatment options moving forward, I think this becomes much more challenging when you're thinking about that risk benefit analysis with a patient. And how many people again, don't have a provider to do that risk benefit analysis. And I'm honestly markedly concerned about how this is all going to roll out moving forward for those who don't have that. So using you know, industry partners who have health care providers who helped to provide health care in that sense, or urgent care is, again, pharmacies who can work with patients to be able to make sure that that is accessible overall. And then the other thing I just wanted to highlight in here is the exhaustion of our healthcare workers, just with the amount of changes everything that it has to learn about COVID. But when there's one more treatment option, one more additional thing they become quite overwhelmed, on how to stay up to date on all of those things. Healthcare systems can be helpful with that. But we also have a lot of people who don't work within healthcare systems. We've stood up in the state of Alaska, you know, a weekly meeting. And we just kind of go through all the literature and try to review for healthcare workers specifically as well as a weekly newsletter just to try to keep them up to date in as many ways as possible because this is just a field that is changing so fast. There's so much demand and so many questions, just try to do what we can to keep them informed. But that's a space where I think we really need to spend some more time and effort thinking about education of healthcare workers moving forward.

Moving on to the next slide. These are some examples from other states and things that they've done regarding monoclonal antibodies. So you know, separate outpatient fusion centers in Alabama and partnering with providing education to providers. Here's many of the same themes here. As mentioned previously, with Dr. Gandhi having a testing and treatment going hand in hand, Maryland put together a network of antigen testing, and trying to co-locate infusions with testing. Similar sorts of things again, Michigan and kind of created regional centers for allocation as we're working with the local and regional healthcare teams. And in Texas, you know, multi stakeholder approach, including healthcare systems, nursing homes, rural hospitals, medical staff companies, and incorporating home infusion and administering right SQ. We've also had drive thru sub Q, and IV infusion sites where people are then watched for a bit of time. So onto the last slide here, just moving forward a couple things, you know, I really appreciate it the beginning, we talked about the challenges with crisis standards of care, and the need for agitations substitution and conservation. But I think something else that we really need to add to that framework is visibility within crisis standards of care, as well as treatment, if we don't have visibility on who needs it and where they need it, then it's hard for us to apply all of these tools. If I have a patient out in Bethel who needs say dialysis or needs treatment, but I don't have good visibility to get them in because say the Anchorage hospitals are completely overwhelmed and they've turned down that patient, then we can't get them the same care. And so I think we need to do more to really build in the infrastructure for visibility on where patients are to make sure that we've got treatment as well as

mechanisms to get people outside of the traditional healthcare system treatment options. We also need to build in visibility with our federal partners, again, IHS, DOD, VA, because while they are separate streams of treatment, they are still the same people working in the same areas. And so making sure that we aren't over resourcing some areas under resourcing others, and building in just better visibility in that partnership. And I really commend HHS and federal government general for building a lot of tools here in a short period of time and looking forward to more so that we have better visibility. Building sustainable treatment infrastructure within as well as outside traditional health care, which we've talked about. And then as mentioned previously, the education and clinical resources, you know, even things like I would love to see something like telehealth where physicians could call and just consult about some of these treatment options or even vaccines, that again, they've just had so much thrown at them in a short period of time that there's not a good place for them to be able to consult on some of this space and so continuing to work on that space. Some of the bigger healthcare systems have it, but some of the smaller ones don't. Again, strategies for responding to COVID-19 surges, including personnel, so not forgetting the personnel. I also think in the crisis standards, care guidelines, personnel is been the biggest limitation that we've seen, really in Alaska and most of the western states. But the guidelines don't really address that they deal with what happens when we ran out of things. But they don't deal very well with what happens when you run out of people. And addressing that personnel issue I think is critical. And then preparing for future pandemic responses and incorporating treatments, not just vaccination, but really building in more of this complex treatment algorithms and streamlining the federal response. So I appreciate the opportunity to be here. And I will hand it back over. Thank you.

Dr. John Hick: Great, thanks so much, Anne. That's a really helpful, you know, context, right there I think as we go into our Q&A here a little bit. We do have a moderator round table, but we invite all of you to come on webcam right now. And we're also joined by Satish Pillai who is represented on the committee formerly known as work speed now medical officer on the Countermeasures Acceleration Group. So I welcome, also Satish. And for those of you attending today, if you could please put your questions into your question box, we will get to as many of those as we are able to today, those that we cannot get to, we will make sure that you get a response in writing from the panel. We'll also have a synopsis of our question and answer period available as a document on the ASPR TRACIE site that archives this presentation shortly after the presentation concludes. So thanks again to the panel for providing a really, really good, you know, sort of level setting here on a number of different areas. So my first question, you know, we've heard a little bit about allocation and clinical prioritization framework that came from NIH in conjunction with IDSA. And Raj, do you want to just present perhaps some of the key conclusions from that really briefly, and then we'll talk about, you know, the specificity level of those and how those need to get translated to a local level?

Dr. Rajesh Gandhi: Sure, I'm happy to walk through the NIH guideline prioritization statement, which start on the next slide, and I'll go through a couple of the key points here.

This is NIH document as opposed to IDSA, just to be specific. So just to start, based on the evidence we started with the panel actually does recommend these monoclonal antibodies for

treatment, and for post exposure prophylaxis in people who are at high risk for progression that is people who meet the FDA EUA. But I really liked the framework that Dr. Hanfling started us out with in terms of thinking about therapeutics. So the NIH statement goes on to say that the monoclonal antibodies are of greatest benefit as treatment or PEP for PEP being post exposure prophylaxis for people who have risk factors for progression. And among those at high risk for progression to severe COVID-19, the risks are lower for those who have been fully vaccinated and are immunocompetent than for those who are either not fully vaccinated or who are fully vaccinated but are immunocompromised people who are not expected to mount an adequate immune response to the vaccine. Let's go to the next slide.

So really what this slide and the next one are really focused on is which individuals might receive the greatest benefit from SARS CoV-2 monoclonal antibodies when logistical or supply constraints make it impossible to offer the therapy to all eligible patients and triage becomes necessary and I think we've heard from Dr. Zink some very good examples of that. And the logistical in our minds is very much personnel as well as space and all the things that go into delivering these antibodies. So the panel goes on to say only when it becomes necessary to triage and unfortunately, we know in many parts of the country it is necessary to triage but only when it becomes necessary to triage the antibodies, the panel suggests treatment of COVID-19 over post exposure prophylaxis of COVID-19. And that it's intended to say and if you is that obviously if someone is exposed and is not symptomatic, if they become symptomatic, and then move into the treatment bucket but prioritizing treatment over post exposure prophylaxis and then prioritizing the antibodies for unvaccinated or incompletely vaccinated individuals as well as and this should also be underlined, I apologize for the misplaced underline. Vaccinated individuals who are not expected to mount an adequate immune response that is immunocompromised or people who are over the age of 65 and I think I saw that Dr. Zink added pregnancy in what they did in Alaska. The fourth point or third point on this slide, providers have to use their clinical judgment because we don't have enough granularity. And the type of granularity we would want to have for all the different risk factors and the last slide will give you some examples. And then I really also like to comment about making sure that there's equitable access and actually tracking that, you know, keeping track of who is receiving antibodies to make sure that we make adjustments if it's not equitable.

And then the last slide and then I'll stop. In addition to the prioritization that I already talked about prioritizing their use for people at highest risk now, the CDC does provide a list of risk factors for severe illness from COVID-19. And we include some of those important risk factors age risks, starting over the age of 50, cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions, obesity, pregnancy and sickle cell. But there is a longer list, as we all know on the CDC website, one thing that we don't have, at least from the CDC is a real clear tearing of risks. There are some states, Utah is one of them, that has developed risk calculators, but there's not in our minds agreed upon universal way to, you know, fully accepted universally way to tier risks. And so we give some examples, and then point to the CDC. And then lastly, if someone has more than one comorbidities, there are data saying that they're at higher risk than if they have a single comorbidity. So if you've got your age is advanced, and you have cancer, you're at greater risk than if you have one of those conditions. So I'll stop there and

acknowledge that we wish we could give more guidance, but this is the framework in which we're kind of operating into.

Dr. John Hick: Thanks, Raj, it's a little bit difficult too because there's so much clinical spectrum amongst a lot of those conditions so that it's really difficult to, you know, make a lot of job broad, sweeping judgments. Anne, translating those recommendations down to you know, the more concrete granular recommendations that Alaska had, how did you do that? What group did you involve? And what process?

Dr. Anne Zink: Yeah, no, thanks. And again, I really appreciate the NIH providing this framework, because it gave a really easy starting place for us to then sit down and say, okay, what does this really mean? Like, where are we at how many cases do we have? And how do we move forward from this? So we had been having a committee that we've used quite a few times throughout the pandemic, initially over kind of approval of the crisis here in secure document last March. And so quite a while ago, at this point, we had a similar group that was stood up for vaccine allocation. But our crisis care committee essentially in the state of Alaska represents every hospital that has an ICU in it just because we're really thinking about capacity, as well as a series of physicians, including ones from rural areas, critical access, tribal hospital, critical access, non-tribal hospital, as well as kind of a group that represents a lot of the inpatient care, both ICU as well as hospitalist. So they're all clinicians, and represent that we meet weekly. And so we brought it to that group. And we said, listen, we're running out of monoclonals, we don't have enough to meet demand. These are the current NIH guidance. What do you guys need? What do you want to do? And they were the ones who brought forward with the pregnancy is it even though it's not listed forward, we feel like that's potentially protecting two people, not just one. And we really feel like that we feel really strongly about that. And here's the additional data. So we went through it. And like you mentioned, there's a lot of clinical guidance and some judgment here for particularly things like immunocompromised. And they settled on if he met criteria for a third for three dose initial series that they wanted to use that as a definition. So we basically took the CDC components, some other data and spaces and tried to just make it a little bit more clinical in that space. And then we rolled out a limited liability protection and just said, this is kind of where we're at. And we've kind of titrate it on and off. Now the cases are coming down with more monoclonals thanks again, to the federal government helping to move things around the state. And we can ask for more, we've been able to actually move off of that and just say, follow the NIH guidance in general. So it was only a couple of weeks that we were in that limited space, and we were able to quickly move off of it and we were able to titrate.

Dr. John Hick: Great, thanks so much, Anne. A question for Jay, the allocation system that you describe, you know, tend to prioritize the states that have you know, highest incidence of disease which means there's a little bit of variability in what states are receiving. Is there you know, anything you can say about you know, planning for you know, these variable levels of you know, therapeutics and what states may need to be prepared for flexibility standpoint. And then also if you can comment on you know, I think Anne brought up a great point that the more dire the situation in the state the more difficult it is to find providers that are qualified to give you know, IV or I even subcutaneous or I monoclonals and might there be an opportunity to prioritize, you

know, some of the hardest hit states for more oral antivirals for example, just give us your thoughts on creating consistency and what you all are trying to do from an ASPR level to help that happen.

Dr. Jay Einstein: Yeah. Well, thank you. Again, the theme is equities and to follow the principles of standard of care and crisis situations. So you know, what we have been doing when products have been initially in short supply shortly after emergency use authorization, we have generally done a baseline allocation, if you will prime the pump. The goal has then been to try to follow the course of need based on disease. And we've done that with a formula that we use where we have a weighted average of newly diagnosed cases and hospitalizations. Basically, we sum a 10th of new cases plus number of hospitalizations, and then each jurisdiction gets its proportionate share of that grand sum. We think that that's what's fair. In terms of the issue of well, there's also the idea, and it was mentioned the importance of a feedback loop, we do look at utilization. And we do look at the inventories that are still present on site. You know, we don't want to simply distribute products where they'll just be hoarded and not used. And we do want to up the allocations where there's evidence that you know, they say, less than three weeks supply and high levels of utilization, so we do make those adjustments. The point is, we do that every single week, that each week, we look at the supplies that are incoming, we look at the utilization from the previous week, and then we allocate using the proportionate formula. But what we have been doing most recently, is when there has been under ordering of the allocated supplies to jurisdictions, we if you will sweep the unused products, and then we offer the jurisdictions to take advantage. If they think they have not been given enough, we engage in a dialogue and we can up their allocation accordingly. So it's a dynamic system. You also mentioned the challenge about, you know, the ability to order and distribute. I think one important thing here is the public readiness and emergency preparedness act declaration that existed to provide liability protection for qualified individuals who can administer COVID-19 therapeutics. And the Assistant Secretary actually, it was the Secretary of HHS, amended the prep act declaration in September, to expand it to licensed pharmacists, who are now authorized both to order and to administer these therapeutics and within the pharmacies, the technicians and the internals. Although they cannot prescribe, they can administer oral subcutaneous and intramuscular preparations, though not intravenous. So these are steps that will have an important value going forward as we move toward the promise of oral antivirals, we'll be able to take much more advantage of what can be done in pharmacies and other health care clinics. So I hope that addressed those questions, John. If I miss something, just come back at me.

Dr. John Hick: No problem. No, that's great, Jay. Thank you. I'm just going to turn this next question to Dan. And with the oral agents on the way. I mean, there's an opportunity here to much more easily provide that therapeutic, you know, to different populations, at risk and otherwise. And there's a bit of a danger that, you know, sometimes too easy access, you go for the low hanging fruit. So how would you say, you know, that we should work towards making sure that as these oral agents roll out that we're making sure that they get targeted to the populations that, you know, are least likely to be able to take advantage in the monoclonals or in areas where the providers or something not available to administer them?

Dr. Dan Hanfling: Yeah, thanks, John. And thanks to all of the other panelists for outstanding presentations. You know, I've learned a lot just being a part of this this afternoon. But I want to

foot stomp, I think Dr. Zink's point about the importance of situational awareness, or what Jay what you, you know, then refer to it as a feedback loop. Now, this is critically important if we are to be able to answer the question, John, that you just asked, which is how to identify those populations who are going to most benefit from the easiest means of administration because of an absence of qualified health care providers, or you know, just the very remote nature of where they are and how it is possible in the supply chain to get an agent where it needs to go. So I think that you know, situational awareness will be critically important. I think that the sorts of principles that were discussed and described with regards to highlighting how to use these agents in treatment or in very, very near term post exposure management, you know, need to be understood by our state partners. And then, again to Dr. Zink's point, hopefully, and I'm guessing that it is the case that every state has convened its ongoing panel of experts who are considering these issues that they will take up, you know, the logistics of having to deliver on the antivirals, particularly oral antivirals. Again, recognizing within their own states, which populations are at most benefit and where is there the staffing need or the staffing you know, barriers that would most lend themselves to an oral agent over parenteral agent.

Dr. John Hick: Thanks. And do you want to come in a little bit? You know, there's always dynamic tension with, you know, these therapeutics, and how much is the public health side responsible for administering these with the Alaska Airlines Center that you set up versus letting these flow through you know, the normal therapeutic channels. Can you comment a little bit about, you know, the balance there? And then also, do you feel like you have enough visibility on say, percent of patients that would have been eligible for monoclonals that receive them in different areas? Or is that just a black hole right now?

Dr. Anne Zink: Oh, man, those are two hot topics. Yeah, so I guess I would say, you know, for the transparency no, I mean, it's really hard to see any sort of transparency and who's getting monoclonals. Even some of our biggest distributors of monoclonals like, don't report in data to us. And so we end up calling them almost every day, like did you give them? Did you not give them? Like, we got to get this information back to HHS to be able to continue to get monoclonals from the state, you know, so we basically have a full time person who's entering data in on who these sites administer for. And we find that the busier people get, the less they reported in. We're also reporting in tons of lab testing. I mean, I think about the thousands and honestly, now millions of negative tests that just are small state has, and how much time that takes. And so then they are like, I'm going to do this first, I'm going to do that later. And I think the reporting aspect, because particularly it's not automated, and it's not electronic for a lot of places, has become just such a big burden. And so I don't think we've got great transparency. To your other question, the first part, you know, the balance, you know, some of the other state health officials, you know, they will tell you, I don't want anything to do with this, get me out of this field as quickly as possible. And this needs to be in the private health care sector, peace out, I got to get out of here. And then you see other states, and we're one of them within the state of Alaska, like, we've got to have visibility, and we have to be involved. Because otherwise, it's not going to get to our rural regions, we're going to have increasing equity, we don't have the private market that's going to be able to stand in this space. So I think that the answer is very diverse, depending on everything from the politics in that region, to the healthcare distribution system in that region, to some of the transport and logistical

areas. You know, I do appreciate with like the H pop system coming out that there's flexibility in that. So the states can be more involved or less involved, I think they heard us loud and clear. That's basically, there we did not have a unified voice and what we need to look at, I think there's just you know, we don't have a unified health care system in Alaska. I think the other people that we need to involve more is the health systems. So we've seen entire health systems so that they are not going to offer vaccination, or they are only going to do this type of treatment and not that type of treatment. And they make that decision for the entire system, which will affect many states. So I think we need to be thinking about how to incorporate them, as well as the pharmacies into this conversation to make sure that they're on board in the same place, because they really are making some of these big decisions about what treatment options are not available, and they have a lot of larger electronic reporting systems that can help us move forward. So I think lots of work to do in this space, where I feel like we're oftentimes duct taping and tying together this broken infrastructure of healthcare and, you know, a practicing emergency physician, you know, we see in the emergency department where all public policy comes to fail, and we see people every single day who show up because the system is not there to support individual patients and their need and trying to connect those pieces together.

Dr. John Hick: Yeah, absolutely, thank you. Raj, can you comment a little bit on timelines for 332 and ACD 7442. You know, when might we see those actually becoming available through an EUA?

Dr. Rajesh Gandhi: You know, I don't know precisely I know that and maybe someone else on this call does, which I would love to hear. But what I know is that the ACD application, the text, whichever maps or Java map application has, I believe, gone into the FDA, I think Jay confirm that. And so I think that's public knowledge that they've submitted. I do know that in Europe, the EMA the European Medicines Association is doing what they call a rolling review of that ACD long acting compound which means product, which means that they, unlike traditional times where the company submits a full application, and then in that case the EMA looks at it here they're willing to receive submissions on a rolling basis so that as data becomes available, the EMA reviews that data. So I think I know the FDA must be reviewing this as to the timeline. I don't know. I think we alluded to the fact that the trial that looked at the effects of this antibody, showed a 77% reduction in symptomatic COVID. But it was largely done in an immunocompetent population. And it was entirely done in non-vaccinated people. And so I think the real question is, will the antibody either that one or Regeneron also is there is some talk about the Regeneron cocktail casirivimab/imdevimab in immunocompromised people. It seems to me and I think probably to most that the real use of these antibodies for prevention, pre exposure prophylaxis, would be on top of vaccines in a population that's immunosuppressed. I think in a non-immunosuppressed population, the priority has to just be to vaccinate. And I don't see this as a substitute for vaccinations, I'd see it as an adjunct for immunocompromised people. The trial didn't study that very extensively. But I do think there's reasons to believe that it should be beneficial in an immunocompromised population. For the 332 drug, I also don't know. I know November 30 is a day that a lot of us are looking towards, because that's the molnupiravir Advisory Committee. I'm not aware if the FDA haven't scheduled an advisory committee for 332, or whether there will be an advisory committee for 332. We all remember that the monoclonal antibodies got authorized

by the US FDA, without an advisory committee. You know, so I don't know what they'll do with 332. I think molnupiravir is getting some discussion a because oral drugs, you know, could be even more broadly used and so by that logic, 332 should also be, you know, go through the advisory committee, but also, some scientists have raised issues around safety with molnupiravir because of that mechanism. And so I think they want a thorough vetting of that issue as well in the advisory committee. So I wish I had a timeline. Does anyone else on this call know? Because if they do, I'd love to hear.

Dr. Jay Epstein: If I knew we couldn't tell you. But I do think that you've hit on a really important point about the potential authorization of ACD 7442, which is we don't really know to what extent the FDA will come forward with broad or narrow intended use indications. And, of course, that's key, you talked about the importance to direct this to not the general population, you know, in lieu of vaccination, but to those who would benefit the most, just to remark that if there is a targeted authorization, it would enable the government as long as we're providing the product through procurements and distribution to target the populations by targeting the administration sites. So we would work with the jurisdictions to identify specialty care centers, for example, you know, oncology clinics, organ transplant centers, etc. where persons with immune compromised get their treatment. We would also expect that education outreach to practitioners in those disciplines would facilitate finding those patients and offering these therapies to them, or I should say these preventatives to them. So you know, it's operating together, but I can't really speak to timeline.

Dr. Rajesh Gandhi: Now, the educational part that was mentioned twice now is key. And I think these ASPR webinars are one example of that. But then also, we also have the ability to access the CDC IDSA clinician calls and I think that's another place I often go to for the latest because this is just too fast for any one person to keep up with. So I think those summaries are good. And I imagine that the pre exposure prophylaxis that betting you know, that education, you know, should also be done to IDSA and CDC and ASPR.

Dr. John Hick: Thank you, Raj. We've got a couple of pretty hot questions here from our audience, which I think are really relevant and very appropriate. And, Dan, because you've expressed an opinion on this in the past, I'll toss it to you the NIH guidance does recommend because of the adverse effects on outcome of unvaccinated status that consideration be given to prioritizing unvaccinated individuals for monoclonal antibody therapy yet, you know, as our questioner points out there offers sort of a perverse incentive, potentially for people to remain unvaccinated. What comments do you have about that?

Dr. Dan Hanfling: Yeah. Look, it's a really difficult question. I think it's a top of mind, particularly on the part of a lot of our colleagues. You know, we're working day in and day out and overburdened health systems. I think, you know, I'll highlight first that Raj correctly, put in all caps vaccination as a strategy. And I think that we need to double down on emphasizing the benefits of vaccination and doing what needs to be done on the education side to address some of the misinformation and other concerns that we think are still serving as barriers. Look, I think that there is potentially a perverse incentive, you know, that some may view with regards to access to monoclonals, and I can't really understand it, right? I mean, I think the vaccines were studied in much greater detail for a much longer period of time than the monoclonals have been, and so I just

don't get it. Without going into all the details, I mean, we can provide some conjecture as to why that has sort of come into play. So you know, what I would highlight is that everybody deserves care. That's our responsibility, the duty to care. And we need to make sure that we are doubling our efforts, redoubling our efforts to provide the information necessary. And to be clear, again, you know, vaccinations look like they are extraordinarily successful, as we know, in keeping people out of the hospital and preventing deaths, the monoclonals, probably not as good. And certainly by the numbers that Raj, you know, shared with us earlier, I think we can make that statement. So part of maybe our strategy going forward on the education front is to be clear, you know, that no, these aren't equivalent, and that they should never be thought of as being equivalent. It's not a magic bullet, it's not the golden ticket, whatever you want to call it. And that's on us collectively, you know as health system, you know, planners, leaders to make those points clear. I'll stop with that.

Dr. Rajesh Gandhi: What I'd like to point out is in the molnupiravir PROVENT study, the group that got molnupiravir still had a 7% hospitalization death rate, which means one out of seven people who got the drug, you know, sorry, seven out of 100 people who got the drug still ended up in the hospital. And so that's vaccines do way better than that in terms of preventing hospitalization. So if we could just get that message, these treatments work, but they don't work as well as vaccines. And so…

Dr. Dan Hanfling: Yeah, and I think, you know, that may be a topic for another ASPR TRACIE discussion, you know, just going head to head but I want to want to come back to Dr. Zink's point about the burnout of the workforce, because our healthcare workforce is suffering day in and day out. And, you know, I understand the rise in frustration that maybe leads to sort of, you know, the recognition of some of these challenges. So we do need to highlight the importance of augmenting and supporting our healthcare workforce, and giving them the tools that they need to be able to, you know, adjudicate some of these decisions going forward.

Dr. John Hick: Agree, increasing their distress by having to make ad hoc decisions doesn't help anybody. So, Raj, I posed this question to you just because you may be privy to some of the backstory on this, I think some of us were a little bit surprised to see in the updated eligibility for monoclonals that race in relation to particularly affected groups could be used as a consideration of, you know, giving monoclonal antibody therapy. Do you have any thoughts? Because the question came in, how should we prioritize that in relation to the physiologic and other indicators for monoclonal therapy? And I'm not sure that we've got a good answer to offer on that. But I also don't know if you or others on the call have the backstory to you know, the FDA, including that.

Dr. Rajesh Gandhi: You know, I don't have this unique insight. I know that the original EUAs listed age, and then a variety of other medical conditions, but in the more recent EUAs they revised that to, I think, emphasize that race and poverty are risk factors for severe outcomes. I mean, I think it has to do with social determinants of health and access to care issues, largely, but I think they wanted to be as Michelle Wollensky said, for vaccines permissive in terms of antibodies, as opposed to restrictive, but then it does create a dilemma when you have to triage because, you know, is it the medical condition and age or is it some social determinant of health? It's a tough one. I don't know that. I would actually love to hear other people's comments and what they think

of that, you know, if we had enough antibodies, I think social determinants of health absolutely are critical to outcomes.

Dr. John Hick: Other thoughts on that?

Dr. Anne Zink: I say, my only thought is like, this is not unique to this, you know, we do this with Tamiflu. We do this for other antivirals and medications. I think it's a complex, I don't think we can fully tear it apart. I know that like in our Pacific Island population, you know, I was meeting with one leader because do people actually not have underlying health conditions like he like literally did not know someone. So that was just like kind of his worldview and what he saw and living multi-generational housing. And what we see with Alaska Native population is just the really high rates that clinically seem to be disconnected to underlying health conditions and social determinants of health. It seems like there's something clinically going on there as well, between both Alaska Native population as well as Pacific Island population, but don't know all the details behind it, we just know that the outcomes are clearly not the same, and need to continue to follow that data.

Dr. Dan Hanfling: Yeah, I was actually going to say, you know, you wrote an excellent piece in The Washington Post, you know, talking about the importance of how we start to plan our recovery, and how we think about the next pandemic, because you know what, we live in an age of epidemics, and there will be a next pandemic. And so this is where I think we need to look at those social determinants of health as a means for figuring out how to improve upon access to care and care delivery strategies going forward. And we have to start now. So you know, and I think that Dr. Wollensky's notion of being permissive is right. But that's easier said and harder to implement right now.

Dr. John Hick: So there are two institutions in shortage. And I think too, I worry a little bit that you know, including, you know, social and racial criteria, and these is not a bad thing, because of the demonstrated outcomes. But in some cases, we've got to be very careful that it doesn't leave us in a position where we say, well, you're eligible, but you can't get it operationally, because we haven't done the work to make sure you can actually get it in your community, you know, in your situation with your mobility or lack of transit, or, you know, whatever it is that the factors are the place that that patient and that population and additional risks. So it's definitely both and they're great. And I think there's a really nice opportunity to, you know, tier testing directly to treatment was some of the, you know, early agents that we really haven't had prior. And do you want to just come in from an operational standpoint, you know, opportunities that you see, you know, to do that now, and how those might be leveraged?

Dr. Anne Zink: Yeah, absolutely. I mean, I think many states will have set up entire structures to be able to set up testing and now with treatment, the opportunity to be able to test someone and get particularly rapid testing back right away so you could educate. I always think about, you know, in emergency departments kind of five steps to crazy, the more barriers that we put between something, someone getting tested, and then be able to get treatment, the more people we're going to lose, particularly those who are high social phobia index are working have a million other things going on as well. And so I think we need to reduce all those barriers, I think the more ways that

we can combine rapid testing with treatment at the same point of care, and then ideally, partner that with where people already are, such as the pharmacy or their industry in their workplace, the more we'll be able to eliminate barriers. And then as previously mentioned, continuing to move upstream and offering vaccines at the same time. So again, when we were doing home monoclonal antibody infusion, they brought with them vaccine and testing. And so people in the household who were not sick offering vaccine right then and there and making it as easy as possible. So I really think we need to reduce those barriers along the stream to be able to move forward. And it's exciting to have one more way to be able to do that.

Dr. John Hick: Absolutely. And you mentioned your program of home infusion. I assume that's using community paramedics and other programs to do that. Do you use that as well for long term care facility residents that are in place and can't move to those facilities? Or what resources can we offer to those long term care residents that continue to suffer?

Dr. Anne Zink: Yeah, it really looks different across the state. So like in Anchorage specifically our pharmacy students have been amazing, and they actually do a lot of our vaccination effort. And then they've been working in combination. There's a private company that used to do our mental health transport, honestly, who said I think there's space for this. And so they stood up a home infusion within kind of the South East most populous area. In other regions, it very much is the home. It's like the EMS and the community paramedics. And so we're really trying to expand that. So along the Kenai Peninsula, they stood this up for vaccination, they said, it doesn't matter who you are, if you've more than two people who need to be vaccinated, we will come to your house and vaccinate and that was great. And then they built on top of that monoclonals and were able to go out and do monoclonals. And then in many of our most rural areas, it's really this community health aides that are doing it. It's been a lot of transportation because there's just not enough to be able to stock most of these places. And so once there's an outbreak, oftentimes what will happen is a hub team will actually fly out to that space. And then they will kind of sweep through the whole area and be able to offer monoclonals, use a lot of antigen testing, like our region publishing MMWR and using antigen testing again, to turn around that turnaround time, we were unable to get the pandemic under control all in this one region until we were able to switch to antigen testing because of the long turnaround time, but now partnering that with treatment, so they're able to fly to a region once a case is identified, and be able to get it out once there's more availability, having it stocked in in a region that doesn't require a flight and weather and all sorts of other transportation logistics that get in the way. But while we're so limited, we're just having to pivot with planes to be able to respond. So it's very different depending where you look at the state.

Dr. John Hick; Yeah, powers of adaptation as always, we'll get us at least halfway there. So I want to thank our panel for an incredible discussion, a lot of great information and turn it over to Audrey Mazurek to close things out. Thank you so much again.

Audrey Mazurek: Great. Thank you so much, John, for moderating today. That is all the time we have for today's webinar. Again, thank you to our panelists. Thank you for participating. This webinar will be archived and posted on our website at asprtracie.hhs.gov. We will send out an

announcement on Monday with the link to the recording and a link to the PowerPoint presentations. On behalf of the ASPR TRACIE team, thank you for joining us today and have a wonderful Friday.