Exhibit 286

FDA Safety Surveillance of COVID-19 Vaccines

Slide 16 Adverse Events

At the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on October 22, 2020 Meeting, Steve Anderson, PhD, MPP Director, Office of Biostatistics & Epidemiology, Center for Biologics Evaluation and Research (CBER) gave a presentation on CBER "Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness".

His presentation included a slide, below, about COVID-19 vaccine adverse event outcomes (injuries and deaths) which the FDA and CDC would be specifically monitoring. But he did not show the slide to VRBPAC, or the viewing public. He clicked right by it.

https://informedchoicewa.org/news/fda-slide-16-table-2-everything-being-reported-to-vaers/

https://www.youtube.com/watch?v=1XTiL9rUpkg

FDA Slide 16 & Table 2: Everything Being Reported to VAERS

informedchoicewa.org/news/fda-slide-16-table-2-everything-being-reported-to-vaers/

September 20, 2021

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At the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on October 22, 2020 Meeting, Steve Anderson, PhD, MPP
Director, Office of Biostatistics & Epidemiology, Center for Biologics Evaluation and Research (CBER) gave a presentation on CBER "Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness".

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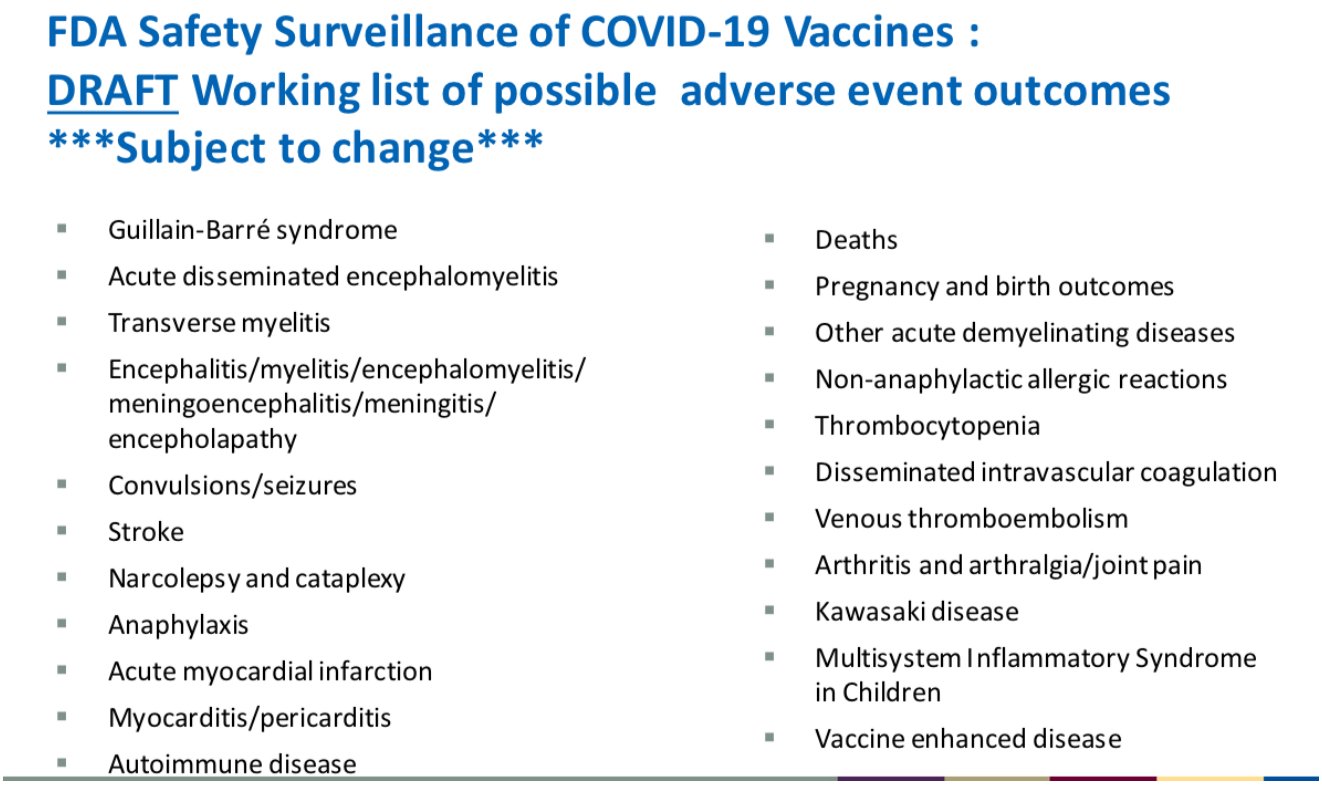
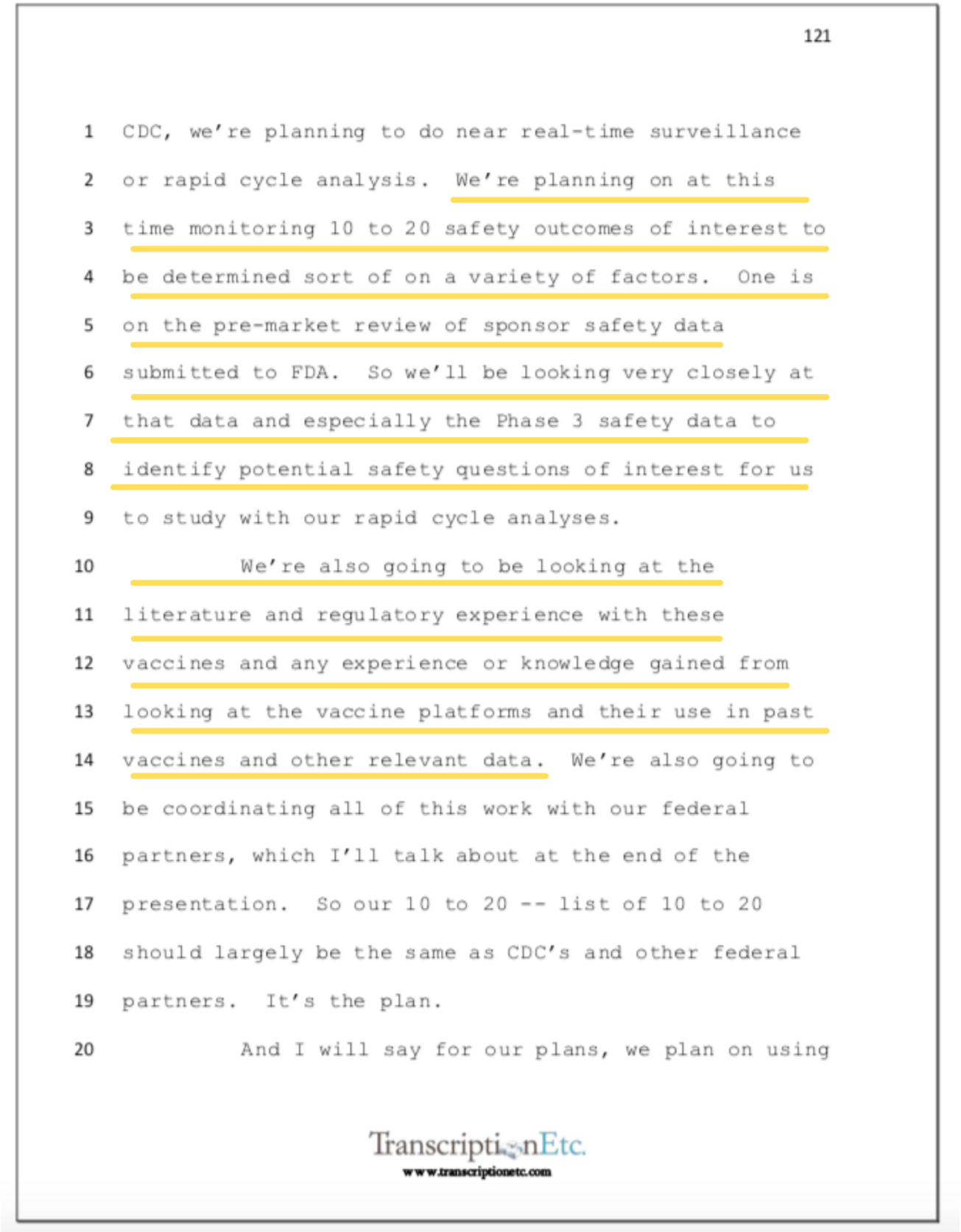


These side effect choices were not random. He explained they were based on evidence from the clinical trial data and from known science on the vaccine platform and components. This is from the transcript of the meeting.



CDC, we're planning to do near real-time surveillance or rapid cycle analysis. We're planning on at this time monitoring 10 to 20 safety outcomes of interest to be determined sort of on a variety of factors. One is on the pre-market review of sponsor safety data submitted to FDA. So we'll be looking very closely at that data and especially the Phase 3 safety data to identify potential safety questions of interest for us to study with our rapid cycle analyses.

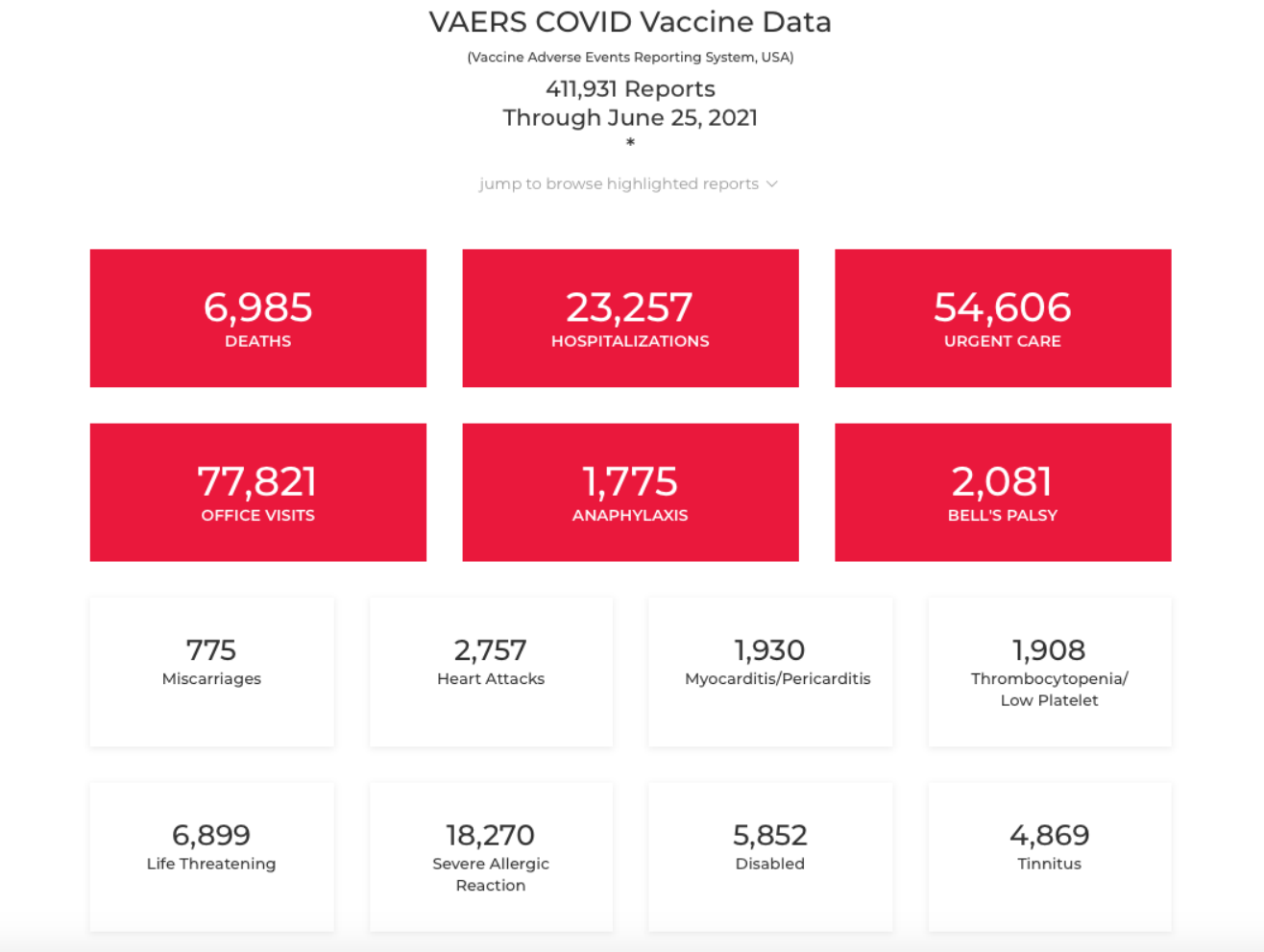
We're also going to be looking at the literature and regulatory experience with these vaccines and any experience or knowledge gained from looking at the vaccine platforms and their use in past vaccines and other relevant data. We're also going to be coordinating all of this work with our federal partners, which I'll talk about at the end of the presentation. So our 10 to 20 -- list of 10 to 20 should largely be the same as CDC's and other federal partners. It's the plan.

And I will say for our plans, we plan on using

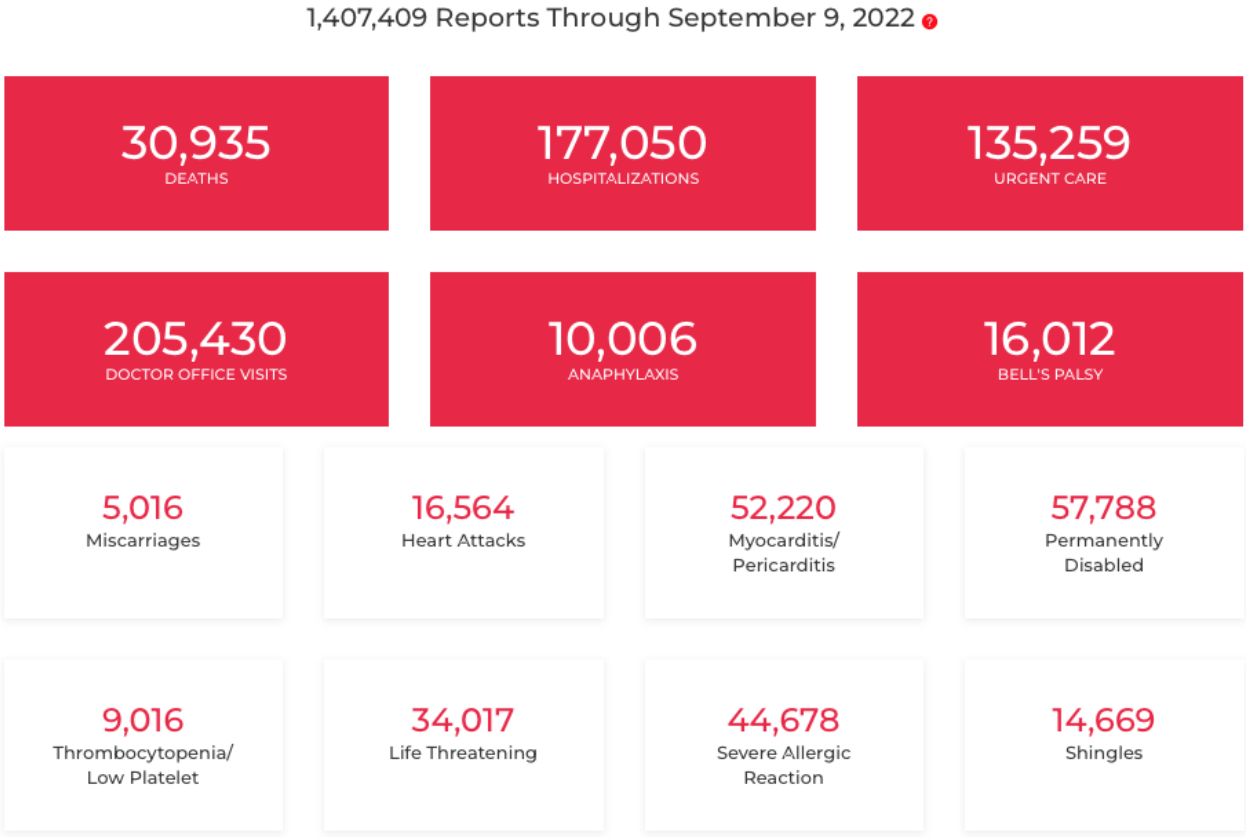
Anderson stated in the above transcript that "we'll be looking very closely at that data and especially the Phase 3 safety tads to identify potential safety questions . . ." However, since he made that statement, the FDA has allowed all of the COVID-19 vaccine makers to unblind

their trials and offer shots to the control group, effectively ending the Phase 3 trials.

These vaccine adverse event outcomes are being reported to VAERS in unprecedented numbers. Here are the numbers from the date of our post in June 2021.



And here are the numbers as of September 9, 2022



In the 2020 VRBPAC presentation, Anderson says that “Tom” also has information about adverse outcomes. By “Tom” he means Tom Shimabukuro of the CDC, and his presentation started at about 1:59 in the video — before Anderson — but Shimabukuro didn’t talk about the information at all and he also clicked right through two slides without pausing. One was a list of vaccine adverse event outcomes they would be looking for in the passive Vaccine Adverse Event Reporting System (VAERS).

Preliminary list of VAERS AEs of special interest

- COVID-19 disease
- Death
- Vaccination during pregnancy and adverse pregnancy outcomes
- Guillain-Barré syndrome (GBS)
- Other clinically serious neurologic AEs (group AE)
  - Acute disseminated encephalomyelitis (ADEM)
  - Transverse myelitis (TM)
  - Multiple sclerosis (MS)
  - Optic neuritis (ON)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Encephalitis
  - Myelitis
  - Encephalomyelitis
  - Meningoencephalitis
  - Meningitis
  - Encephalopathy
  - Ataxia
- Seizures / convulsions
- Stroke
- Narcolepsy / cataplexy
- Autoimmune disease
- Anaphylaxis
- Non-anaphylactic allergic reactions
- Acute myocardial infarction
- Myocarditis / pericarditis
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Venous thromboembolism (VTE)
- Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
- Kawasaki disease
- Multisystem Inflammatory Syndrome (MIS-C, MIS-A)

The other was a list of vaccine adverse event outcomes they would be looking for in CDC's Vaccine Safety Datalink System (VSD). The public and most independent researchers have no access to this data for independent review.

Preliminary list of VSD pre-specified outcomes for RCA

- Acute disseminated encephalomyelitis (ADEM)
- Acute myocardial infarction (AMI)
- Anaphylaxis
- Acute respiratory distress syndrome (ARDS)
- Arthritis and arthralgia / joint pain
- Convulsions / seizures
- Disseminated intravascular coagulation (DIC)
- Encephalitis / myelitis / encephalomyelitis / meningoencephalitis / meningitis / encephalopathy (not ADEM or TM)
- Guillain-Barré syndrome (GBS)
- Immune thrombocytopenia (ITP)
- Kawasaki disease (KD)
- Multisystem Inflammatory Syndrome in Children (MIS-C)
- Myocarditis / pericarditis
- Narcolepsy / cataplexy
- Stroke
- Transverse myelitis (TM)
- Venous thromboembolism (VTE)

The FDA has a new system launched in 2017 (a full decade after FDA Amendments Act of 2007 that required them to create an active postmarket risk and analysis system covering at least 100 million persons) called Biologics Effectiveness and Safety (BEST) System. The

BEST system is now being used to try to establish background rates for the COVID-19 vaccine “Adverse Events of Special Interest” that the CDC and FDA will be monitoring with their systems.

Table 2. List of Adverse Events of Special Interest (AESIs)

Safety AESI	Age Group of Interest	Care Setting	Clean Window**
General Population Outcomes			
Guillain-Barré syndrome	All	IP- primary position only	365 days*
Facial nerve palsy	All	IP, OP, PB	183 days*
Anaphylaxis	All	IP, OP, PB	30 days
Encephalomyelitis	All	IP	183 days*
Narcolepsy	All	IP, OP, PB	365 days*
Appendicitis	All	IP, OP-ED	365 days*
Non-hemorrhagic stroke	All	IP	365 days*
Hemorrhagic stroke	All	IP	365 days*
Acute myocardial infarction	All	IP	365 days*
Myocarditis/pericarditis	All	IP, OP, PB	365 days*
Deep vein thrombosis	All	IP, OP, PB	365 days*
Pulmonary embolism#	All	IP, OP, PB	365 days*
Disseminated intravascular coagulation	All	IP, OP-ED	365 days*
Immune thrombocytopenia	All	IP, OP	365 days*
Transverse myelitis	All	IP, OP-ED	365 days*

Given that global data analysis has shown a possible association between seasonal flu vaccination and COVID-19 disease severity, it’s interesting that the BEST study says:

> To estimate incidence rates of AESIs in special populations of interest stratified by calendar year, sex, age group, and race/ethnicity (where reliably available) in each data source over the period 2017–2020. These populations will include:
>
> o Older adults(i.e.,65 years old and abovea tcohort entry)
> o Pediatric population(i.e.,0–17 years old at cohort entry)
> o Pregnant women
> o **Individuals who received a seasonal influenza vaccine in the previous calendar year**

During this COVID-19 crisis, both the FDA and CDC have made decisions that have not been in the best interest of the population or individuals. They have approved investigational products without sufficient safety or efficacy data, and they have actively censored or ignored existing treatments and natural immunity. They are actively partnering with the COVID-19 vaccine makers.

There are two important aspects of establishing whether reported adverse events are related to receipt of a vaccine. One is epidemiological. The rates of certain health issues in the general population are compared to the rates in people getting vaccinated. That's what the FDA's BEST study is about. Obviously, this information alone cannot rule causation in or out. Biological studies are also needed. Can the product cause the outcome seen? Ever since the 1986 National Childhood Vaccine Injury Act passed, removing liability from vaccine makers for injury or death for products recommended to children and pregnant women, the CDC has been in charge of vaccine safety and utterly failed in their duties. Biological studies are almost non-existent. The CDC prefers to use weaker epidemiological studies that are easily manipulated to desired outcome, to try to claim reported events are not associated.

Will they do the same for the COVID-19 vaccines? If so, will they get away with it? Since we first wrote that question, it has been answered. Yes, the federal oversight agencies are using contrived epidemiological studies, avoiding biological studies of their own while ignoring very concerning independent studies that are revealing the mechanisms of action that lead to harm. To find the latest, search Pubmed using keyword "COVID-19 vaccine" and an injury reported to VAERS, such as myocarditis, tinnitus, Guillain-Barre syndrome, Bell's Palsy, etc.

Fortunately during COVID, researchers around the world have been awakened to the capture and corruption of public health agencies and they are beginning to do their own, independent studies. They are starting their own journals that have no ties to governments or the drug industry. A revolution is beginning within the ranks of doctors and scientists who believe in honest and ethical science and medicine.

Post References:

Tom Shimabukuro's slides: https://www.fda.gov/media/143530/download

Steve Anderson's slides: https://www.fda.gov/media/143557/download

Video of the meeting: https://youtu.be/1XTiL9rUpkg

Meeting transcript: https://www.fda.gov/media/143982/download

FDA page with links to all materials: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-22-2020-meeting-announcement#event-materials

BEST Background Rate study: https://www.bestinitiative.org/wp-content/uploads/2021/01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf

Vaccines and Related Biological Products Advisory Committee October 22, 2020 Meeting Presentation

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CBER Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness

Steve Anderson, PhD, MPP
Director, Office of Biostatistics & Epidemiology, CBER

VRBPAC Meeting
October 22, 2020

FDA Vaccine Surveillance: Pre-licensure Pharmacovigilance Planning

"Safety throughout the lifecycle" approach for vaccines (pre- and post-licensure):

- Manufacturer submits pharmacovigilance plans (PVP) of proposed post-licensure surveillance activities
  - Submitted for BLA and for EUA
  - Post-licensure commitment (PMC) – studies, registries for general safety concern
  - Post-licensure requirement (PMR) – clinical study, epidemiological study, registries, etc. to verify a specific safety signal
  - Routine pharmacovigilance – Passive surveillance (VAERS), review of safety literature, available studies, etc.

FDA Vaccine Surveillance Programs: Post-Licensure

1. **Passive Surveillance of Vaccines**
   - Vaccine Adverse Event Reporting System (VAERS)
     - Management shared by CDC and FDA

2. **Active Surveillance Monitoring Program**
   - FDA BEST
   - FDA-CMS partnership

FDA Vaccine Surveillance Programs: Post-Licensure

1. **Passive Surveillance of Vaccines**
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VAERS

Vaccine Adverse Event Reporting System

Co-managed by CDC and FDA

CDC + FDA

http://vaers.hhs.gov

VAERS – FDA CBER Efforts

- CDC presentation covered VAERS so will provide summary of FDA efforts
- **FDA and CDC have weekly and bi-weekly coordination meetings** on VAERS and Pharmacovigilance activities between CBER OBE and OBE Division of Epidemiology (DE) and CDC Immunization Safety Office
- **CBER DE Physicians will be reviewing the serious adverse event reports** from VAERS for COVID-19 vaccines – review of individual reports, death reports, conduct aggregate analyses, case-series, etc.
- **FDA will utilize statistical data-mining methods** to detect disproportional reporting of specific vaccine-adverse event combinations to identify AEs that are more frequently reported

FDA Vaccine Surveillance Programs: Post-Licensure

1. Passive Surveillance of Vaccines
   - Vaccine Adverse Event Reporting System (VAERS)
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FDA Vaccine– Legislative Authorization Active Surveillance

Legislation, mandates and Current Surveillance

FDA Amendments Act of 2007:

- Directed FDA to develop an active risk identification and analysis system – such as Sentinel, and later BEST, and others and covers ≥100 million persons

Prescription Drug User Fee Act VI (2017)

- Discussion between FDA and Industry on Priority Areas - Renewed every 5 yrs
- Provides resources/funding for Sentinel, BEST, real-world evidence, etc

COVID-19 Vaccine Monitoring Data Considerations

- **Rapid data access** for near real time surveillance
- **Large databases of tens of millions of patients** for evaluating vaccine rare serious adverse events
- **Data representing integrated care spectrum** – outpatient, physician, inpatient, etc.
- **High quality data** to assess and confirm potential adverse events or safety concerns for COVID-19 vaccines
- **Data with significant clinical detail** or medical chart access

1. FDA Biologics Effectiveness and Safety (BEST) System

- Several partners – Acumen, IBM Watson, IQVIA, OHDSI, HealthCore, Humana, Optum, Healthagen, Academic organizations
- Represents variety of healthcare settings – inpatient, emergency department, outpatient, etc.

BEST Initiative Expansion

CLAIMS Data Sources

Data Sources	Type	Patients (millions)
MarketScan	Claims	254
Blue Health Intelligence	Claims	33.6
Optum	Claims	70
HealthCore	Claims	56
Healthagen	Claims	26
OneFlorida Clinical Research Consortium (Medicaid)	Claims	6.7

Data lag: 1-12 months depending on data source

BEST Initiative Expansion
EHR Data Sources

Data Sources	Type	Patients (millions)
MedStar Health	EHR	6
IBM Explorys	EHR	90
Regenstrief Institute	Claims and EHR	20.2
Columbia University	EHR	6.6
University of Colorado	EHR	17
University of California San Francisco	EHR	3.2
PEDSnet Clinical Research Consortium	EHR	6.2
Optum EHR	EHR	105
OneFlorida Clinical Research Consortium	EHR	5.6
OneFlorida Clinical Research Consortium	Linked EHR-Claims	1.5
MarketScan Explorys Claims-EHR (CED)	Linked EHR-Claims	5.5
Optum	Linked EHR-Claims	50

Data lag: 1-2 weeks to 4 months depending on data source

2. CMS (Center for Medicare & Medicaid Services)

- **Federal Partners**
  - Ongoing FDA-CMS partnership on vaccine safety since 2002
  - Data cover very large population of approximately 55 million elderly US beneficiaries ≥65yrs of age
  - >92% of US elderly use Medicare so database represents the elderly population and not a sample
  - Represents variety of healthcare settings – inpatient, outpatient, etc.
  - Consists of claims data with access to medical charts

Limitations of Data Systems

- Not all claims and EHR data systems can be used to address a vaccine safety or effectiveness regulatory question

- Each data system has its limitations
  - Populations, healthcare settings, clinical detail, necessary parameters, data lag, exposures and outcomes that are captured

FDA COVID-19 vaccine safety surveillance planning

“Near real-time surveillance” or rapid-cycle analyses (RCA)

- FDA plans on monitoring 10 -20 safety outcomes of interest to be determined based on:
  - Pre-market review of sponsor safety data submitted to FDA
  - In coordination with federal partners, international regulatory partners and organizations, academic experts, others
  - Literature and regulatory experience with similar vaccines, novel vaccine platforms, and using other relevant data
  - FDA plans on using CMS data for COVID-19 vaccine RCA – near real time with efforts

FDA Safety Surveillance of COVID-19 Vaccines :
DRAFT Working list of possible adverse event outcomes
Subject to change

- Guillain-Barré syndrome
- Acute disseminated encephalomyelitis
- Transverse myelitis
- Encephalitis/myelitis/encephalomyelitis/ meningoencephalitis/meningitis/ encepholapathy
- Convulsions/seizures
- Stroke
- Narcolepsy and cataplexy
- Anaphylaxis
- Acute myocardial infarction
- Myocarditis/pericarditis
- Autoimmune disease
- Deaths
- Pregnancy and birth outcomes
- Other acute demyelinating diseases
- Non-anaphylactic allergic reactions
- Thrombocytopenia
- Disseminated intravascular coagulation
- Venous thromboembolism
- Arthritis and arthralgia/joint pain
- Kawasaki disease
- Multisystem Inflammatory Syndrome in Children
- Vaccine enhanced disease

FDA Experience with Near Real Time Surveillance / RCA

FDA and CMS - RCA

- Conduct "near real-time" surveillance for annual influenza vaccine and Guillain-Barre Syndrome(GBS) since 2007
- Support confirmation of CDC rapid-cycle analyses of safety for seasonal influenza vaccine, Shingrix, and others

FDA Sentinel – Rapid Surveillance

- Near real-time, rapid surveillance in 2017-2018 seasonal influenza vaccine – evaluation of 6 health outcomes of interest

FDA COVID-19 vaccine safety surveillance Plans

- **Epidemiological analyses**
  - Need capability to resolve potential safety signals identified from near real-time surveillance, TreeScan and other sources
  - Rapid queries and small epidemiological studies
  - Larger self-controlled, cohort, comprehensive protocol-based studies

COVID-19 Vaccine Effectiveness Surveillance Plans

- COVID-19 vaccine(s) – there may be limited information available at licensure on level and duration of effectiveness
- Manufacturers may conduct certain COVID-19 vaccine effectiveness post-licensure studies
- FDA may conduct COVID-19 vaccine effectiveness studies
  - General effectiveness studies – including subpopulations of interest
  - Duration of protection studies
  - Others
- FDA coordinating COVID-19 Vaccine Effectiveness efforts with the CDC NCIRD through monthly, bi-monthly meetings

FDA-CMS-CDC Vaccine Effectiveness Experience

- Extensive experience with the data and methods needed to conduct vaccine effectiveness studies
- Produced several vaccine effectiveness and relative vaccine effectiveness studies for influenza and zoster vaccines
- Conducted duration of effectiveness analysis of Zostavax vaccine

FDA-CMS Vaccine Effectiveness Experience

- Actively studying risk factors for COVID-19 and preparing to study safety and effectiveness of vaccines and biologics therapies
- More than 30 publications since 2012
- Results included in Congressional testimony

CBER COVID-19 Vaccine Monitoring Transparency Considerations

- Master Protocols for Safety and Effectiveness outcomes
- Posting of draft protocols for public comment
- Posting of final protocols and final study reports on the BESTinitiative.org website

US Government-wide Efforts COVID-19 Vaccine Monitoring

Large US Government Effort

FDA Coordinating its COVID-19 vaccine safety and effectiveness monitoring efforts with other government agencies:

- Centers for Disease Control (CDC)
- Centers for Medicare& Medicaid Services (CMS)
- Veterans Administration (VA)
- National Institutes of Health
- Department of Defense
- Indian Health Services

US Government-wide Efforts
COVID-19 Vaccine Monitoring (2)

Large US Government Effort

- Weekly meetings between FDA and CDC, regular meetings with VA and CMS
- Planned sharing of protocols, discussion safety and effectiveness outcomes of interest
- Coordinated planning and conduct of surveillance activities such as near real time surveillance/ RCA between FDA, CDC, CMS, VA, and DOD

Acknowledgments

- Richard Forshee
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- CBER Surveillance Team
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- CBER OBE Colleagues
- CDC Colleagues
- CMS Colleagues
- VA Colleagues
- FDA Partners: Acumen, IBM Watson – and new partners in FY2021

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
161st Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Via Web Conference

October 22, 2020

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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Mike Kawczynzski	Food and Drug Administration

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OPENING, CALL TO ORDER, INTRODUCTIONS

MR. KAWCZYNSKI: Good morning and welcome to the 161st meeting of Vaccines and Related Biological Products Advisory Committee meeting. I'm Mike Kawczynski from FDA, and I will be today's meeting facilitator. Throughout today's meeting, I'll be reminding our presenters and OPH speakers when they are close to their allotted time and assisting them when needed. This is a live virtual public meeting. At this time, I'd like to introduce Dr. Arnold Monto, the acting chair. Dr. Monto, please turn on your camera and take it away.

DR. MONTO: Thank you, Mike. I'd like to first welcome everybody to this virtual meeting, which is going to discuss in general the development, authorization, and/or licensure of vaccines to prevent COVID-19. This meeting is virtual, and we will be following standard practices of the VRBPAC Advisory Committee.

I'm very pleased to chair this meeting. And it's a return from me because I just rotated off this committee last January, and I'm very pleased to be able to help in providing input on this very important topic to the FDA. I'd like to turn the meeting introductions and the other material -- the administrative details, over to Dr. Atreya who will continue. Dr. Atreya.

ANNOUNCEMENTS, ROLL CALL, COI STATEMENT

DR. ATREYA: Good morning, everyone. I hope you can all hear me well. My name is Prabha Atreya, and it is my great pleasure to serve as the designated federal officer for today's 161st Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA's Center for Biologics Evaluation and Research and the Committee, I would like to welcome everyone to today's virtual meeting.

Before we begin with formal roll call and reading the Conflict of Interest statement, I would

like to briefly make a few administrative remarks and housekeeping items related to today's virtual meeting. For everyone using the public doc view link access available from the FDA meeting page, there is a separate link included for anyone in need of close captioning. For members, speakers, FDA staff, anyone joining us in the Adobe room, to minimize the feedback, please keep yourself on mute unless you are speaking. Also please turn on your video if you are presenting, commenting, or asking a question to maintain the bandwidth level throughout the meeting. Lastly, if you raise your hand and are called upon to speak by Dr. Monto, please state your first name, last name, and speak slowly and clearly so your comments will accurately be recorded for transcription. Please do not log out of the meeting or disconnect your phones during the breaks. Otherwise, you will have to have to be reapproved to join back in.

Let's begin today's meeting by taking the formal roll call for the standing Committee members,

followed by temporary voting members. When it is your turn, please turn on your camera, then state your first name and last name, your organization, and your expertise for the benefit of the public. All right. When finished, please you can turn off your camera so we can proceed to the next person. Let's start the roll call. Let's see. Dr. Monto, can you start please?

DR. MONTO: Right. I'm Arnold Monto. I'm Professor of Public Health and Epidemiology at the University of Michigan School of Public Health. Besides infectious disease epidemiology, I've worked extensively in clinical trials of influenza vaccines and other vaccines and anti-virals. I've also had experience working in observational studies which tell us how well vaccines work when they're applied to the public. But the real reason I'm here at this meeting is because I've been working on and off for about 30 years with coronaviruses, and I actually was in Beijing during the SARS outbreak.

DR. ATREYA: Okay. Thank you, Dr. Monto. Dr. Amanda Cohn, can you start? Introduce yourself.

CAPT. COHN: Yes, good morning. I'm Dr. Amanda Cohn. I'm the Chief Medical Officer of the National Center for Immunizations and Respiratory Diseases at the CDC in Atlanta. I'm a pediatrician who has expertise in vaccines and infectious diseases, and I've been at the CDC for about 16 years.

DR. ATREYA: Great. Thank you. Dr. Chatterjee, would you introduce yourself, please?

DR. CHATTERJEE: Yes, good morning. My name is Archana Chatterjee. I am a pediatric infectious diseases specialist, like Dr. Cohn, and currently serving as the dean of the Chicago Medical School, as well as Vice President for Medical Affairs at Rosalind Franklin University in Chicago. My expertise is in the realm of pediatric vaccines. I have been a clinical scientist and conducted over 110 clinical trials, about half of those in pediatric vaccines. Thank you.

DR. ATREYA: Thank you, Dr. Chatterjee. Dr.

Meissner, could you introduce yourself, please?

MR. KAWCZYNSKI: Let's see. Who should be up? Cody should be up next.

DR. ATREYA: Yes. Yes.

MR. KAWCZYNSKI: Cody, go ahead and unmute yourself. I got it. There you go, sir.

DR. MEISSNER: I apologize for the delay. My name is Dr. Cody Meissner. I'm a Professor of Pediatrics at Tufts University School of Medicine. I'm also the Director of the Pediatric Infectious Disease Division at Tufts Hospital for Children. I have had a long-standing interest in vaccine clinical trials, in vaccine safety, and vaccine effectiveness. I have participated in the Advisory Committee on Immunization Practices for the CDC, and I continue to work with the Committee on Infectious Disease for the American Academy of Pediatrics.

DR. ATREYA: Thank you. Dr. Gans, can you introduce yourself, please?

MR. KAWCZYNSKI: Dr. Gans, you'll have to

unmute yourself.

DR. ALTMAN-GANS: Hi. I'm Hayley Gans.

MR. KAWCZYNSKI: There you go.

DR. ALTMAN-GANS: And I am a professor of pediatrics and pediatric infectious disease at Stanford University. My work focuses on the host-pathogen interface using vaccines to look at the immune system in pediatrics, as well as in special populations such as our immunocompromised folks. Thank you.

DR. ATREYA: Excellent. Thank you. Dr. Kurilla, would you introduce yourself, please?

DR. KURILLA: Good morning. Michael Kurilla. I am the Director of the Division of Clinical Innovation at the National Center for Advancing Translational Science within the National Institutes of Health. Prior to that, this position which I've had for almost three years, I was at the National Institute of Allergy and Infectious Diseases focused on infectious disease product development for a biodefense and immerging infectious diseases. Before that, I had

several stints in industry and an academic career that included both basic research in viral immunology and clinical microbiology. I'm a pathologist by training.

DR. ATREYA: Thank you. Dr. Paul Offit, can you introduce yourself, please?

DR. OFFIT: Sure. My name is Paul Offit. I'm a professor of pediatrics in the Division of Infectious Diseases at the Children's Hospital in Philadelphia and the University of Pennsylvania School of Medicine. My expertise is in the area of vaccine infectious diseases, and I'm the co-inventor of the bovine/human reassortment rotavirus vaccine, RotaTeq. Thank you.

DR. ATREYA: Thank you. Dr. Annunziato, would you introduce yourself, please?

DR. ANNUNZIATO: Good morning. I'm Paula Annunziato. I'm the vaccine clinical development for Merck. Merck is one of the few companies that has discovery, development, and manufacturing in both vaccines and antivirals. I'm here today as the non-voting industry representative.

DR. ATREYA: Thank you. Mr. Sheldon Toubman, would you introduce yourself?

MR. TOUBMAN: Yes. Good morning. My name is Sheldon Toubman, and I am an attorney at New Haven Legal Assistance Association in New Haven, Connecticut. I've been there for 29 years, but most of my work is in the area of access to healthcare on behalf of low-income individuals -- children and adults -- and particularly in the Medicaid program. I am here today as the consumer representative for the Committee.

DR. ATREYA: Dr. Pergam, would you introduce yourself?

DR. PERGAM: Thanks, everyone. I'm Steve Pergam. I'm an infectious disease physician and Associate Professor at the Fred Hutchinson Cancer Research Center and at the University in Washington in Seattle, Washington. My expertise is in infectious disease epidemiology with a special focus on the immunocompromised population.

DR. ATREYA: Great. Dr. Beckham, would you

introduce yourself?

DR. BECKHAM: Hi. My name is Dr. Beckham. I'm the office director for the Office of Infectious Diseases and HIV/AIDS Policy within the Office of the Assistant Secretary for Health. I've been in this role about two years. Previous to that, I held several roles in academia, leading centers of infectious diseases, and also worked at the United States Medical Research Institute on Infectious Diseases as well. I'm a D.V.M., PhD in vaccine, and I'm here today as a member. Thank you.

DR. ATREYA: Great. Now I will introduce the temporary voting members. Starting with Dr. David Wentworth.

DR. WENTWORTH: Good morning. My name is Dave Wentworth, and I'm a PhD in virology. And I am currently the Chief of the Virology Surveillance and Diagnostics Branch in the Influenza Division at the CDC. I'm also our WHO Collaborating Center director. I have expertise in virology, particularly influenza

and coronaviruses.

DR. ATREYA: Excellent. Thank you. Dr. Hildreth, would you introduce yourself, please?

DR. HILDRETH: Good morning. I'm James Hildreth. I'm the president and CEO of Meharry Medical College. I'm also a professor of internal medicine. My expertise is in virology and immunology. For the last 30 years, I've been studying HIV. My focus really is on viral pathogenesis and how the immune system deals with pathogenic viruses. Thank you.

DR. ATREYA: Excellent. Dr. Jeannette Lee, would you introduce yourself?

DR. LEE: Yes. Good morning. My name is Jeannette Lee. I'm a professor of biostatistics at the University of Arkansas for Medical Sciences at Little Rock. My area of expertise is leading data coordinating centers for multicenter clinical trials in HIV and auto-infectious diseases, cancer, and pediatrics. Thank you.

DR. ATREYA: Okay. Thank you. Dr. Kathryn

Holmes, would you introduce yourself?

DR. HOLMES: Yes. I'm Kathryn Holmes, Professor Emerita from the University of Colorado School of Medicine in the Department of Microbiology, and Immunology. I have spent the last 40 years before my retirement studying coronaviruses, in particular in spike glycoproteins and the receptors with which they interact. I'm interested in the host-range determinates of coronaviruses and how viruses become able to jump from one host to another and cause epidemics.

DR. ATREYA: Great. Thank you. Dr. Luigi Notarangelo, would you introduce yourself? You're on mute.

DR. NOTARANGELO: Good morning. My name is Luigi Notarangelo, and I'm the Chief of the Laboratory of Clinical Immunology and Microbiology at the National Institute of Allergy and Infectious Diseases at NIH. Before that, I was Professor of Pediatrics at Harvard Medical School. My expertise is in pediatrics,

immunology, and genetics. I contributed to the discovery of genetic endemiological determinates of severe COVID-19.

DR. ATREYA: Okay. Thank you. Dr. Michael Nelson, would you introduce yourself?

DR. NELSON: Hi. Good morning. I'm Dr. Michael Nelson, recently retired from active duty service in the United States Army Medical Corps. I'm Professor of Medicine at the Uniformed Services University and currently a practicing physician at Walter Reed National Military Medical Center. I'm also President of the American Board of Allergy and Immunology, certifying allergists and immunologists nationwide. My expertise, if you will, is I was at ground zero for the development of the bioterrorism vaccine program and continue to work with rare adverse events to vaccines within the military health care system. And in my specialty of allergy and immunology, we also are fundamentally interested in primary and secondary immune deficiencies. Thank you.

DR. ATREYA: Thank you. Dr. Perlman, would you introduce yourself?

DR. PERLMAN: Yeah. Hi. I'm Dr. Stanley Perlman, Professor of Microbiology and Immunology and a pediatric infectious diseases specialist at the University of Iowa. I've worked with coronaviruses for nearly 40 years, working on the immune responses in people and in animals and in animal models of (audio skip).

DR. ATREYA: Okay. Great. Thank you. Now we will do introductions for FDA staff. Dr. Gruber, Dr. Krause, and Dr. Weir, Dr. Fink, if you would like to introduce yourself, this is the opportunity and please feel free to turn your cameras on if you would like.

DR. GRUBER: Good morning. My name is Marion Gruber, and I'm the Director of the Office of Vaccines Research and Review at the Center for Biologics Evaluation and Research. Thank you.

DR. ATREYA: Dr. Krause.

DR. KRAUSE: Hi. I'm Dr. Phil Krause. I'm

the Deputy Director of the Office of Vaccines Research and Review at FDA CBER.

DR. ATREYA: Dr. Weir.

DR. WEIR: Hi. I'm Jerry Weir. I'm the Director of the Division of Viral Products in the Office of Vaccines in CBER, FDA. Thanks.

DR. ATREYA: Thank you. Dr. Fink.

DR. FINK: Hi. Good morning. This is Doran Fink. I am the Deputy Director for Clinical Review in the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research at FDA.

DR. ATREYA: Very good. Thank you. Thank you all for your introductions. I would also like to acknowledge the presence of Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research, and Dr. Celia Witten, Deputy Director for the Center for Biologics Evaluation and Research. Would you like to introduce yourselves? Okay. So maybe they will join a little later.

Now, I would like to introduce my excellent staff -- Ms. Kathleen Hayes, who is my backup DFO for this meeting, and, if I am unable to conduct the meeting for any reason, she will be able to do so. Ms. Christina Vert is also a DFO providing support for this meeting. The committee management specialist for this meeting is Ms. Monique Hill, and the committee management officer for this meeting is Dr. Jeannette Devine, who provided excellent administrative support, COI screening and preparing for this meeting today.

The topic for today's meeting is to discuss in general the development, authorization, and/or licensure of vaccines to prevent COVID-19. Today's meeting and the topic was announced in the Federal Register Notice that was published on August 28, 2020. The FDA press and media representative for today's meeting is Ms. Abigail Capobianco, and the transcriptionist is Ms. Linda Giles.

Now, I will proceed with reading the Conflict of Interest statement for the public record. The Food

and Drug Administration is convening virtually today on October 22, 2020, the 161st meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Dr. Arnold Monto is serving as the acting voting chair for this meeting.

Today, on October 22, 2020, the Committee will meet in open session to discuss the development, authorization, and/or licensure of vaccines to prevent COVID-19. This topic is determined to be of particular matter involving specific parties. With the exception of the industry representative, all standing and temporary voting members of the VRBPAC are appointed special government employees or regular government employees from other agencies and are subjected to federal Conflict of Interest laws and regulations.

The following information on the status of this Committee's compliance with federal Ethics and Conflict of Interest laws including, but not limited to, 18 United States Code Section 208 is being provided

to participants in today's meeting and to the public. Related to the discussions at this meeting, all members; RGEs, regular government employees; and special government employees, SGEs, and consultants of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and, for the purpose of U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, cooperative research, and development agreements (CRADAs), teaching, speaking, writing, patents, royalties, and primary employment. These may include interests that are current or under negotiations as well.

FDA has determined that all members of this advisory committee are in compliance with the federal Ethics and Conflicts of Interest laws. Under 18 U.S.C. Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular

government employees who have financial conflicts of interest when it is determined that the Agency's need for the special government employee services outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be determined likely to affect the integrity of the services which the government may expect from the employee. Based on today's agenda and all financial interests reported by Committee members and consultants, there have been two Conflicts of Interest waivers granted under 18 U.S.C. 208 in connection with this meeting.

We have the following consultants serving as temporary voting members: Dr. Jim Hildreth, Dr. Michael Nelson, Dr. Kathryn Holmes, Dr. Stanley Perlman, Dr. Jeannette Lee, Dr. David Wentworth from CDC, and Dr. Luigi Notarangelo from NIH. Among these consultants, Dr. James Hildreth and Dr. Jeannette Lee -- both special government employees -- have been issued

waivers for their participation today. These waivers were posted on the FDA website for the public disclosure.

Dr. Paula Annunziato is currently serving as the industry representative, and she's employed by Merck. Industry representatives are not appointed as special government employees and serve as only non-voting members of the Committee. Industry representatives act on the behalf of all regulated industry and bring general industry perspective to the Committee. A non-voting industry representative may not discuss his or her employing company's position as such but may discuss any matters in general terms. Industry representatives on this Committee are not paid, do not participate in any closed sessions we have, and do not have voting privileges.

Mr. Sheldon Toubman is serving as consumer rep for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation. They are

voting members of the Committee and, hence, do have the voting privileges.

Today's meeting has multiple external speakers. We have four speakers from the Center for the Disease Control and Prevention. These are Dr. Lawrence Clifford McDonald, Dr. Tom Shimabukuro, Dr. Stephanie Schrag, and Capt. Janell Routh. One speaker, Dr. Hilary Marston, is from the National Institute of Health. Another speaker is Dr. Robert Johnson. He is employed by the Biomedical Advanced Research and Development Authority, BARDA, within HHS. The guest speaker for this meeting is Dr. Susan Winckler, who is the Chief Executive Officer of the Reagan-Udall Foundation for the FDA. She will be supported by Ms. Chrisanne Wilks.

Regular government employee speakers Drs. McDonald, Marston, Drs. Johnson, Shimabukuro, Schrag, and Routh have all been screened for conflicts of interests and have been cleared to participate as speakers for today's meeting. Disclosures of conflicts

of interest for guest speakers follow applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants including open public hearing speakers to advise the Committee of any of the financial relationships that they may have with any of the affective firms, its products, and, if known, its direct competitors.

We would like to remind the standing and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a special or imputed conflict of interest, the participants need to inform the DFO and exclude themselves from such involvement, and their exclusion will be noted from the record. This concludes my reading of the Conflict of Interest statement for the public record. At this time, I would like to hand over the meeting back to our chair, Dr. Monto. Dr. Monto, the meeting is yours now. Thank you.

DR. MONTO: Thank you very much, Prabha, and I

would like in turn to introduce again Dr. Marion Gruber, who is the director of the Office of Vaccines Research and Review, who will give the Committee its charge. Marion.

FDA INTRODUCTION

DR. GRUBER: Yeah. Good morning again. On behalf of my colleagues in the Office of Vaccines and in CBER, I would like to welcome the Committee members and the public to today's meeting. We look forward to a robust and productive discussion on today's topics, which include the data needed to support approval or an Emergency Use Authorization of the COVID-19 vaccines. Of note, we will not be discussing any specific COVID-19 vaccine candidates today.

I want to take a minute to assure the American public that facilitating the development of safe and effective COVID-19 vaccines is the highest priority of my office, CBER, and the Agency. Today's discussions

will provide transparency about the data that we will request and evaluate in support of the safety and effectiveness of these vaccines. And discussing these in today's topic forum is critical to build trust and confidence in the use of COVID-19 vaccines by the general public and the medical community.

The development, the authorization, and licensure of vaccines against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks. Numerous COVID-19 vaccine candidates are currently in development, and these vaccines are based on different platforms, including mRNA and DNA vaccines, subunit vaccines, inactivated vaccines, non-replicating and replicating viral vectors, live attenuated vaccines, and virus-like particles. Most COVID-19 candidate vaccines express the spike proteins or parts of the spike protein -- that is the receptor binding domain as their immunogenic determinant.

Now, while most of these vaccines are in early

stages of clinical development, some have advanced to Phase 3 clinical trials in the U.S. and globally to evaluate their efficacy and their safety. COVID-19 vaccine development may be accelerated based on knowledge gained from similar products that are manufactured with the same technology, and some vaccine manufacturers are using these approaches. Vaccine manufacturers are also using adaptive or seamless clinical trial designs for their vaccine studies, which would allow for more rapid progression through the usual phases of clinical development.

The FDA must ensure that the vaccines that are approved or authorized as investigational products under Emergency Use Authorization are supported by the best available scientific and clinical evidence and that the legal requirements for safety and effectiveness are met. The Office of Vaccines is facilitating the development of COVID-19 vaccine candidates by conducting expedited reviews of the CMC information, preclinical and clinical protocols, and

clinical trials data. We also provide timely advice and guidance and have frequent interactions with vaccine developers to expedite proceeding to Phase 3 clinical trials. And we also engage in efforts to ensure that adequate data are generated to support access to investigational COVID-19 vaccines.

COVID-19 vaccines will likely be widely deployed and administered to millions of individuals, including healthy people. And the public can expect that U.S. licensed COVID-19 vaccines are effective and safe and there's a low tolerance for vaccine-associated risks. COVID-19 vaccines that are licensed in the United States must meet applicable legal requirements, and the FDA will apply the same standards to grant a biologics license for a COVID-19 vaccine as for other preventive vaccines.

The Office of Vaccines, in collaboration with our colleagues in the Office of Biostatistics and Compliance, will ensure that these standards are met by conducting a thorough review of the data and

information submitted. And we will make our regulatory decisions based on these data. The review is conducted by a multi-disciplinary team of clinicians, statisticians, research scientists, and other subject-matter experts. Many of us have decades of experience in vaccines regulations and regulatory science.

Vaccine development can be expedited. However, I want to stress that it cannot and must not be rushed as it takes time to accrue the adequate manufacturing, safety, and effectiveness data for these vaccines to support their use in millions of healthy people. And thus, the Office of Vaccines will not reduce its scientific rigor or standards and regulatory decision making regarding COVID-19 vaccines.

The single set of regulatory requirements applies to all vaccines, regardless of the technology used to produce them. Section 351 of the Public Health Service Act states that, "The biologic license application shall be approved based on a demonstration that the biological product... is safe and pure and

potent and the facility in which the biological product is made meets standards designed to assure that the biological product continues to be safe and pure and potent." And what that means is that only those vaccines that are demonstrated to be safe and effective and that can be manufactured in a consistent manner will be licensed by the FDA. Our regulation states further that, "... all indications that will be listed in a product's package insert must be supported by substantial evidence of effectiveness." And this evidence is derived from adequate and well-controlled clinical studies.

For COVID-19 vaccines, considering the current trajectory of the pandemic and the current lack of an immune marker that will predict effectiveness, the goal of development programs at this time should be to generate data necessary to support FDA licensure by conducting clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infections and/or disease. I want to stress again

that the overall development strategy and the data that are required to support licensure of COVID vaccines are no different than what would be required for other preventative vaccines if they're licensed by the FDA or are currently in development. Each vaccine, however, may have specific issues to be addressed during development.

For a COVID-19 vaccine to be approved, a manufacturing process needs to be developed that ensures product quality and consistency. Product-related data and testing plans that are adequate to support the manufacturing process in an appropriate facility, to characterize product stability, and to ensure consistency of its manufacture are needed. We need nonclinical data to characterize the nonclinical safety and immunogenicity and, for COVID-19 vaccines, data to address the potential for vaccine-induced enhanced disease.

Now, enhanced disease associated with human coronaviruses, such as MERS-CoV and SARS, have so far

only been demonstrated in animal model vaccinated with MERS and SARS vaccine candidates and then subsequently exposed to the respective wild-type viruses. It is not known whether this phenomenon occurs with SARS-CoV-2. But, nevertheless, it needs to be evaluated as part of COVID-19 vaccine development.

We need human clinical data that are adequate to support the proposed indication and use, which means adequate safety and efficacy data need to be accrued. And in addition, we encourage vaccine manufacturers to also characterize the clinical immune response that is induced by a vaccine. Data are needed demonstrating that the facility that the product is made is in compliance with current good manufacturing practices, and a post-licensure pharmacovigilance plan is needed.

The FDA developed and published, in June 2020, a guidance for industry document to help facilitate the timely development of safe and effective vaccines to prevent COVID-19. This guidance reflects advice the FDA has provided over the past several months to

companies and researchers and others. It describes the Agency's current recommendations regarding the data that are needed to facilitate clinical development and licensure of vaccines to prevent COVID-19. And these will be presented in more detail this afternoon by my OVRR colleagues.

Turning to Emergency Use Authorization now, based on the declaration by the Secretary of Health and Human Services over a public health emergency that involves the virus that causes COVID-19 earlier this year, FDA may issue an Emergency Use Authorization -- or EUA -- after it has determined that certain statutory requirements are met. Of note, an EUA is different from product approval. During an EUA, the FDA can authorize the emergency use of unapproved -- that means investigational products -- to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents such as COVID-19 when there are no adequate approved or available alternatives.

In order to issue an EUA, the FDA must determine, among other things, that the product may be effective and that the known and potential benefits of the investigational product outweigh its known and potential risks. Use of an investigational COVID-19 vaccine under an EUA is not subject to informed consent requirements. However, vaccine recipients need to be provided a fact sheet, and that describes the investigational nature of the product, the known and potential benefits and risks of the product, available alternatives, and there is the option to refuse vaccination.

An EUA for a COVID-19 vaccine may allow for rapid and widespread deployment for administration of the investigational vaccine to millions of individuals, including healthy people. And therefore, issuance of an EUA for an COVID-19 vaccine will require adequate manufacturing information to ensure the quality and consistency of a product, and a determination by the FDA that the vaccine's benefit outweighs its risks will

be based on data from at least one well-designed Phase 3 clinical trial that demonstrate the vaccine's safety and efficacy in a clear and compelling manner. Any assessment regarding an EUA --

MR. KAWCZYNSKI: Doctor, we have about three minutes left.

DR. GRUBER: Thank you. Any assessment regarding an EUA would need to be made on a case-by-case basis considering the proposed target population, the characteristics of the product, the preclinical and human clinical data on the product, as well as the totality of the available scientific evidence that's relevant to the product.

Now, earlier this month, the guidance that the Office of Vaccines had generated -- and this entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" -- was issued. It reflects advice the FDA has been providing to vaccine developers, and it describes FDA's recommendations regarding the manufacturing, preclinical and clinical data that would

need to be submitted to support an EUA request, and issuance of an EUA for a COVID-19 vaccine. These will be presented, again, in more detail this afternoon by my OVRR colleagues.

So turning for a minute to today's agenda, we hear next a presentation by the CDC on the epidemiology, virology, and clinical features of COVID-19. Then, there will be two presentations by the NIH and BARDA, each talking about their respective activities in the development of vaccines against COVID-19. Then, we'll hear presentations on CDC's plans for safety and effectiveness, monitoring, and evaluation during EUA use and post-licensure. There will be next a presentation on CBER surveillance systems and another presentation by the CDC on the operational aspects of COVID-19 vaccine distribution and tracking.

After lunch, there is a presentation by the Reagan-Udall Foundation on COVID-19 vaccine confidence. And then my FDA colleagues will present on CMC and

clinical consideration on licensure and Emergency Use Authorization of vaccines to prevent COVID-19. Following the open public hearing, there will be the committee discussion and recommendations.

Now, to guide the Committee's deliberation, we have prepared the following discussion items. Of note, the Committee is not asked today to vote on any issues discussed. Discussion item one, please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents. Two, please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine. Three, please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to, A, further evaluate safety, effectiveness, and immune markers of protection; and, B, evaluate the safety and effectiveness in specific populations.

And this concludes my introduction. Thank you very much, Mr. Chairman.

DR. MONTO: Thank you very much, Marion. You've given us a clear background of what we are to examine today and what we will be discussing later on in the evening. Because of the time constraints and because we're going to be getting back to these issues just before the public meeting, I'd like to move on and call Dr. Cliff McDonald from CDC to give us the epidemiology, virology, and clinical features of COVID-19.

EPIDEMIOLOGY, VIROLOGY, CLINICAL FEATURES - COVID-19

DR. McDONALD: Good morning. My name is Dr. Cliff McDonald from the CDC. I'm an adult infectious disease trained physician and medical epidemiologist. I'm currently serving as the Chief Medical Officer for the CDC's coronavirus response. I would like to begin by thanking the program organizers for this opportunity to share our current understanding of the rapidly evolving COVID-19 pandemic. I have no financial

disclosures, and I would like to acknowledge Dr. John Brooks, who has served as the Chief Medical Officer for the CDC response to date, for his instrumental work in the preparation of these slides.

I'd like to start with a brief overview of basic coronavirus virology, which is, of course, attributing to the type of virus that causes COVID-19. Coronaviruses are single-stranded RNA viruses. They are on the large end of viruses, both in terms of their size and in terms of their genomes. The coronavirus genome encodes four major structural proteins including the spike protein, shown here in gray. The spike protein is the part of the virus that binds the cells and facilitates viral fusion with the cell and cell entry. These spike proteins form a crown-like halo that is the characteristic feature of coronaviruses.

And here is the star of our show. This image is an electron micrograph of an actual coronavirus, albeit not SARS-CoV-2. But this stand-in is a good example that nicely shows off the characteristic crown-

like halo.

Coronaviruses are Nidovirales and infect a wide variety of mammals and birds. The term "nido" comes from the Latin word nidus for nest and refers to hallmark of the nidovirus transcription seen also in all coronaviruses, namely the synthesis of a three-prime coterminal nested set of mRNAs. Coronaviruses are divided into four genera: alpha, beta, gamma, and delta. The alpha and beta coronaviruses are in mostly mammals and include the coronaviruses that cause human disease, which I'll cover in the next slide.

They have been isolated from many land mammals as well as those that fly, like bats, and those that swim, like beluga whales. The gammas and deltas infect mostly birds and have been isolated from birds across the entire size spectrum from sparrow to ostrich. Coronaviruses can cause a variety of lethal disease in mammals and birds and have been well studied due to their impact on the agricultural sector where they cause fatal disease in the form of respiratory and

enteric diseases.

Of the seven coronaviruses known to cause human disease, or HCoVs for short, four generally cause mild disease, mostly upper respiratory illness such as the common cold. However, three of these have these pathogens -- all beta coronaviruses -- can cause lethal human disease. These include SARS-CoV-1, the cause of the 2003 SARS outbreak; MERS-CoV, first recognized in 2012 and that continues to cause sporadic clusters in the Middle East Respiratory Syndrome; and now SARS-CoV-2. So that we're all on the same page, I want to make sure everyone understands, we use the term COVID-19 to describe the illness caused by the SARS-CoV-2 virus, and it is named SARS-CoV-2 because it is genetically more like SARS-CoV-1 than MERS-CoV.

Let me just share with you what we know about transmission of COVID-19. As the initial outbreak in China resolved, COVID-19 was spreading rapidly worldwide. COVID-19 has now been reported basically everywhere except for a few island nations and

Antarctica. Worldwide, new diagnoses are now rising after a period of relative stability, with the largest expansion right now occurring in Southeast Asia shown here in purple.

Note that as of Tuesday October 13th, the total number of infections worldwide is rapidly approaching 38 million and that the daily number of new infections are between 300,000 and 400,000, which is three times the 115,000 diagnoses made during the entire first six weeks of the pandemic when it was mostly limited to China. That now appears as the very modest-appearing pink blip at the far bottom left of the figure. Despite the expansion in Southeast Asia and the recurrent expansion in Europe -- shown in light green -- the U.S. still accounts for the largest fraction of cumulative number of cases at 22 percent and of deaths at 21 percent, followed by India that has accounted for 17 percent of the world's total cases, then Brazil at 15 percent, and Russia at 4 percent.

Looking now specifically at the United States,

new cases are rising again since around Labor Day after a period of decline from a mid-summer peak. Deaths are presently stable, but, given the rise in new cases and the time from diagnosis to death to then officially reporting that death, we have been watching closely for any signs of an increase. In fact, since this slide was prepared, we have seen a two percent increase in deaths over the past seven days compared to the previous seven days.

Presently, we are seeing 50,000 to 60,000 new cases a day and about 700 deaths. Far too many American are still being infected with and dying from this preventable infection. We have plenty of work ahead, and we cannot let down our guard.

Despite the close genetic relatedness of SARS-CoV-2 to its cousins, SARS-CoV-1 and MERS-CoV, this new virus differs from both of its relatives in two important ways. First, although the incubation periods are all about the same, persons with COVID-19 from SARS-CoV-2 infection can be infectious to others and

transmit the virus before they develop symptoms. We now know that infectiousness peaks in the few days before and then during symptom onset. Second, a substantial fraction of infected persons, estimated at perhaps 15 to 45 percent, never develop symptoms and remain asymptomatic. We know that these persons can also transmit the infection, although how infectious they may be to others is still being worked out.

This table shows what we presently know about which body fluids carry and may transmit SARS-Cov-2, showing whether viral RNA has been detected, whether actual viruses has been isolated in culture, and whether the body fluid has been epidemiologically documented as a mode of transmission. It is very clear that SARS-CoV-2 causes a respiratory illness transmitted through exposure to respiratory particles. Although viral RNA can be readily detected in stool, efforts to isolate virus from stool by culture have been remarkably unsuccessful with only a handful of reports suggesting possible isolation of live virus

amid many reports of failed attempts. Moreover, if stool is a mode of transmission, it has yet to be epidemiologically confirmed.

In blood, viral RNA can be detected, but reassuringly it does not appear to contain virus that can be cultured. And no infections have been documented through blood product transfusion. Curiously, detection of RNA has been confirmed in semen but only in men during the peak of illness. After recovery, RNA appears to no longer present. And neither isolation of live virus nor sexual transmission of SARS-CoV-2 has been reported. Lastly, neither viral particles nor virus have been found in urine.

Depicted on this slide are results of an ongoing large scale of serosurveillance activity in partnership with commercial laboratories in which the aim is to perform serology on 1,000 specimens from each state on waste serum specimens from persons who had blood drawn for other reasons. These data are available on CDC's COVID data tracker and are the most

recent available results. As of August 2020, New York, New Jersey, and Louisiana are the only states with over 10 percent of the population with antibody levels indicating a past infection.

The darker shades of pink or purple here indicate higher prevalence of past infection. I will caveat these findings with the fact that, in some patients with past infections, there may be a decay in the antibody levels, and some do not develop an antibody response. That decay, however -- it's unclear how much that might cause a reverse into negativity.

I will also further caveat the seroprevalence findings with the fact that the role of serology is still evolving. The utility of serologic testing to establish the absence -- sorry -- the clinical utility of serologic testing to establish the absence or presence of infection or reinfection as well as immunity remains undefined. Although, as suggested by the previous slide, this doesn't prevent it from being an important component of public health surveillance.

Data that will inform serologic testing guidance -- the serologic testing guidance area is rapidly evolving. Serologic or other correlates of immunity have not yet been established since serologic testing should not be used clinically to establish presence or absence of infection, as I mentioned, or reinfection or immunity.

I'd like to move on now to describe how we're responding clinically to infections with SARS-CoV-2, and I want to do this by emphasizing four main points. First, viral burden declines steadily after illness onset. As shown in these two figures with the y-axis showing viral load and the x-axis showing time since illness onset, the amount of viral RNA measured in clinical samples is greatest with the onset of illness and then declines steadily as time passes. Second, as shown in the upper figure, as viral load is declining after illness onset, the ability to recover live virus from human samples by culture becomes less likely.

After eight to ten days, we can no longer recover replication-competent virus, so that is virus

from culture from respiratory tract specimens in otherwise healthy persons with mild to moderate illness. A recent study suggests that severely ill persons who often might spend weeks in the hospital can shed live virus up to 20 days. Third, within days after illness, patients begin to develop a serologic or antibody response to infection that includes IgM, IgG, and IgA.

And the IgG response includes neutralizing antibodies that can block viral infection in cells in laboratory assays. Although our immune systems are clearly responding to and controlling the infection, we don't know at this time how well this immune response protects us from reinfection, and, if it does, for how long. Not all persons develop antibodies after infection, as I mentioned earlier, and early data does suggest some decay or decline in these antibodies as early as eight weeks after infection.

The good news is now approaching nine months following major spread outside China, we have

relatively few instances of documented reinfection. The bad news, of course, is that there have now been a handful and growing number of well-documented reinfections, with the first of these in a person initially infected in Hong Kong who recovered and who then became asymptomatically infected after returning from a trip to Spain. However, the frequency of these reinfections is still uncertain, and overall, they appear quite infrequent when we consider the large number of infections. Reinfections should not be surprising given experience with the other endemic human coronaviruses.

Fourth and lastly, it has now been widely observed that viral RNA can be detected by PCR for weeks, long after persons have been fully recovered from illness, and after evidence would indicate they're no longer infectious. Shown here is an illustrative decay curve from a paper by Xiao et al. that illustrates the classic reverse sigma slope seen with this phenomenon. To date, the longest persistent

positive has been documented at 12 weeks. And, as I mentioned earlier, reinfections, when they do occur and have been documented, they most likely appear to occur after three months or 90 days, and during this 90-day interval, we are no long recommending PCR testing.

Mindful of time, I'll keep moving on. The clinical epidemiology -- I'll just highlight a few facts of this. First and foremost, just to mention here the relative frequency of major signs and symptoms observed. These are from early reports in China. More than 80 percent of patients develop fever during illness; over half develop cough; about 25 percent myalgia or arthralgia; and in a small fraction, headache, which is mentioned; also the loss of smell and taste, which is probably one of the most distinguishing factors. Although, it can also be seen with other respiratory illnesses.

Given our time, I'll just mention the mortality, case fatality rates here as seen. It goes up sharply in older age groups but understand that this

is seen with other respiratory illnesses. Still, the case fatality rate is about 10 to 15 times that of influenza.

Because of the time, I'll just jump to mention that NIH has published severity of illness categories, which are important because they are linked to some treatments, and mention some of these underlying illnesses that do largely increase morbidity and mortality along with age as shown on the previous slides. I want to also mention that the distribution of underlying illnesses that increase the case fatality rate are not evenly distributed across the United States -- and finally, just mention as you know, unfortunately, there's long standing healthcare inequities and much of this has manifested through different rates of underlying chronic illnesses but also then increase the case fatality rate in different ethnic groups. So with that, I'll end. Thank you.

MR. KAWCZYNSKI: All right. Dr. Monto, are you there? I just want to make sure your audio's still

connected. I think your audio may not be connected at the moment, Dr. Monto. With that being said, since we did run out of time on that one, Prabha, would you like me to move onto the next presenter while we are waiting for Dr. Monto to connect his audio?

DR. ATREYA: From NIH?

MR. KAWCZYNSKI: Yep. So the next person would be -- next up is Hilary Marston.

NIH ACTIVITIES IN THE DEV OF VACCINES - COVID-19

DR. MARSTON: Thank you so much for the opportunity to speak to you today about the role that the NIH plays in COVID-19 vaccine development. So my name is Hilary Marston. I'm a medical officer and policy advisor for pandemic preparedness in the Office of the Director at NIAID. Next slide. I don't think I have control here.

MR. KAWCZYNSKI: Yep, bottom of the screen. There you go.

DR. MARSTON: Ah, thanks so much. Sorry about that. Okay. So I'd like to speak today about three different aspects of our work in COVID-19 vaccine development: so, first, moving from preparedness to response, our activities in basic and translational research; second, our work in Phase 3 trials and our efforts to create harmonized clinical trials; and third, within those trials, our key priorities, and some future directions.

So first, basic research moving from pandemic preparedness to response -- so when cases of this new pneumonia syndrome first came to light in the beginning of January 2020 and when researchers shared the genetic sequence of this new virus on international databases on January 10th and it was reported one day later, we had researchers who were ready to jump into vaccine development. And they had a specific approach that they wanted to take to vaccine development. The reason why they were so primed to this work is because the NIH had made a long-term investment in pandemic

preparedness response research and preparedness research, basic and translational.

So specifically, these researchers had worked on this family of beta coronaviruses. We knew from both SARS and MERS that this family had the potential to cause epidemics, and we knew that they could, in some cases, be spread by a respiratory route, which is obviously one of the key features of a pathogen that would cause a potential pandemic. So we wanted to focus on this group, along with other pathogens that we work on quite closely.

In this paper in *PNAS*, we describe a specific body of work that we have on this group of viruses whereby we have a specific solution to creating vaccines for them. So we take the protein that's on the outside of the virus. We stabilize it in the genetic sequence by making two specific mutations and use that as the vaccine antigen. Animal studies on MERS show that this approach made the protein far more immunogenic in mice. And we were able to show that the

same two mutations if carried into other related viruses could create the same stable immunogenic antigen.

So as soon as the sequence was shared on international databases, our researchers were able to look at that sequence. The researchers are listed here: Kizzmekia Corbett and Barnie Graham and our vaccine research center along with some colleagues. They were able to make those changes that they wanted to make to make that stabilized antigen, share it with our industry partners at Moderna -- we had a preexisting research collaboration with them -- and the Moderna researchers were able to put it into their rapid manufacturing platform. And 65 days later, we were able to start a Phase 1 trial. But critically, that was enabled by the long-term investments in basic preparedness research.

I should also say that that early manufacturing was supported by the Coalition for Epidemic Preparedness Innovations who has been an

excellent partner in this work. So we were not the only ones who jumped into action in developing vaccines. In fact, there are now six vaccine candidates supported by the U.S. government in advanced clinical development. My colleague from BARDA is going to tell you more about these candidates, so I'll just go over them briefly.

So there are two in the mRNA category. These are the Moderna and the BioNTech/Pfizer candidates. The advantage of the mRNA platform is that it offers very rapid manufacturing, which facilitates a quick move into the clinic, and they are highly immunogenic.

There are two adenovirus vectored candidates from AstraZeneca and Janssen. Again, these are quite quick to get into the clinic. And the platform itself, in the case of Janssen, is used in a vaccine that's approved in Europe, their Ebola Virus vaccine.

And then we adjuvanted recombinant protein vaccines. So they're not as fast to manufacture, but they are very scalable, tend to be quite stable. And

there are several approved vaccines that use this approach. Those are Novavax and Sanofi in partnership with GSK.

So I mentioned that we were able to launch into a Phase 1 trial in March 2020, and other candidates moved in quite quickly as well. So all of these candidates are now in Phase 1 and some in Phase 2 trial -- and some indeed in Phase 3. The Phase 1 and 2 trials have overall shown that the vaccines are quite safe, immunogenic, and well tolerated, also that they have good binding antibody titers and viral neutralization titers that are comparable to those seen in human convalescent sera.

So with those data and with that human experience, we were confident that we were ready to move into larger scale trials, but we wanted to make sure that we had harmonized those clinical trials. We wanted them to be individual trials that we could move as quickly as possible. But we also wanted to make sure that they were harmonized so we would be able to

compare across the trials.

So we laid out a specific strategy for these trials in this commentary that was published in May 2020 by leaders at the NIH along with a leader of one of our large clinical trials networks, the HIV Vaccine Trials Network. The key characteristics of the harmonization are shown in this figure from the paper. So again, these are going to be individual trials as depicted as the top of the slide, but clinically, they're going to be harmonized with respect to endpoints, with respect to statistical analysis plans for example.

They will all use collaborating clinical trials networks, which I'll describe in just a moment. They'll all use collaborating labs. So for key immunogenicity assays, these are going to be run by NIH and NIH-supported labs. So those will be the serology that distinguish SARS-CoV-2 infection from a vaccination, the neutralization assays, and the T-cell response assays.

And this is important. They share an independent data and safety monitoring board -- so one data and safety monitoring board which is comprised of long-standing vaccine experts, and they are able to look at the data in an unblinded fashion, oversee the scientific integrity of the trial, and to safeguard volunteers. And importantly, because they can look across the trials, they can look out for anything that seems out of line, anything that seems unusual with respect to the cases that are seen. And then there's also a between-trial statistical group that's looking at correlates of protection.

The clinical trials network that I mentioned, this is actually comprised of multiple clinical trials networks, which are from the NIH and the Department of Defense. Collectively, the investigators in these networks have decades of experience in clinical trials and large-scale clinical trials for infectious diseases. So they came together recognizing the urgency of the public health emergency and created a

new entity called the COVID-19 Prevention Network.

A little bit about the governance of these trials, so again the vaccine companies are the IND sponsors. Each trial has clinical trial sites that are provided by both contract research organizations contracted to the company and the COVID Prevention Network -- that clinical trial network that I just mentioned. Each of the companies -- each of the trials report into this independent data and safety monitoring board, which offers its recommendations to an oversight group, and the oversight group is comprised of representatives from NIH, BARDA, and shared by the company/sponsor.

Just a little bit more detail on the NIH ~~roll~~ there, so again the company is the regulatory sponsor under 21 CFR 312. The Phase 3 trials, the protocols were designed in collaboration with Operation Warp Speed, with the NIH, and specifically the active partnership under the NIH -- that public/private partnership -- the CoVPN, and they all conform to FDA

guidance. The trials are overseen by that Data and Safety Monitoring Board for which NIH serves as the secretariat. The NIH, along with the active partnership, offered the names for that DSMB. The NIH supported investigators at the CoVPN offered both trial sites and network investigators or co-PIs in the trial. NIH sits on that oversight group, so we're at each level of the trial structure.

A bit on the trials themselves, so these are all randomized, placebo-controlled efficacy trials with either a one-to-one or two-to-one vaccine to placebo match. The sample size varies somewhat, but they are anywhere from 30,000 to 60,000 volunteers. The primary efficacy endpoint has a point estimate and requirement of greater than 60 percent. And the lower bound of the confidence interval must be greater than 30 percent.

The population, so these are individuals over 18 years of age, and we're specifically in reaching for people who are at risk of severe disease, so whether those are individuals who are elderly or have

comorbidities or are from underserved minorities. One notable exception to this is the Pfizer trial, which is run independently. They are now enrolling down to age 12.

The primary endpoint of the trials is prevention of symptomatic COVID-19 disease, which is PCR confirmed. Importantly, all identified cases are assessed for severity and followed to resolution of the case. So while it might start off mild, we will document how severe that the cases get. And all clinical case data are submitted in an unblinded fashion to both the DSMB and to the shared biostatistical group.

Some specifics on the safety follow up in the trial, so the primary safety objective is to evaluate safety and reactogenicity of vaccines. For seven days, we're looking at solicited local and systemic adverse reactions; twenty-eight days, we're looking at unsolicited adverse events; and then, at any time in the two-year follow up, for medically attended adverse

events, adverse events of special interest as outlined in the protocol, and severe adverse events at any time. So all adverse events are reviewed by a dedicated safety team, and they're reviewed in an unblinded fashion by the DSMB. For severe AEs, there's a more thorough review that's specifically conducted by the DSMB. And the DSMB is going to be looking at all times for imbalances in severe COVID cases between study arms.

So now some key priorities for these trials and I'd like to speak about three specific areas: so, the first being safeguarding volunteers; second, enrolling individuals who request the pandemic and particularly individuals who are at risk of severe COVID; and the third is generating and maintaining trust with the public. So first, safeguarding volunteers, so we are developing vaccines in a public health emergency. We recognize the urgency of it. We, as overall in Operation Warp Speed, are willing to take financial risks, particularly with respect to

manufacturing and investing in manufacturing earlier than one might otherwise. But the scientific integrity of the trials and the volunteer safety are not compromised.

So I wanted to specifically address some of the safety pauses and holds in the trials. Adverse events are expected to occur in these trials in both the vaccine and placebo groups. These are monitored and graded for severity using standard procedures, and these are regularly reviewed by study clinicians and monitors and protocol safety teams to ensure proper interpretation and reporting as needed. So in other words, we are finding these events because we are specifically looking for them, and we are looking for them according to tried and true processes.

In addition, there are multiple layers of safety oversight, including the company's own pharmacovigilance -- this should say the NIH-led Protocol Safety Review Team -- the DSMB, and the FDA. These are all in place to protect study volunteers.

It's something we take very seriously.

I would say that the recent regulatory hold for AstraZeneca and the clinical pause for Janssen are signs that the system is working as expected. We're finding these cases. We are working them up thoroughly and working in close partnership with the regulators over at FDA.

Next, enrolling those at highest risk of infection and severe disease, so it is critical that, at the end of these trials, we have reliable, interpretable data on the safety and efficacy of these vaccines in those who are hardest hit by the pandemic. So who is that? We know, as described by the prior speaker, that those individuals who are in older age groups are at risk for severe disease and those individuals who have specific comorbidities. In addition, we know that individuals from underserved minorities are hit harder by this pandemic, both in terms of infection and in terms of severe disease and, indeed, death.

So we know that we need specific information in these groups. Our trials have parameters that are explicit on enrollment of volunteers with these individual risk factors, so, for example, whether it's individuals over age 65, people with comorbidities, or people of specific underserved minorities. And in order to do the latter, we've been working hard on proactive community engagement activities, and this really has been a top priority for NIH leadership at the highest levels. These measures are critical to the success of the trials themselves, but they're also going to allow assessment of safety and efficacy in the populations that are at highest risk. And we know that's going to be essential for future acceptability of these vaccines.

Some specifics on our activities in these areas, so first the Community Engagement Alliance Team, this is an NIH entity that's drawing on long-standing relationships that we have at our clinical trial networks at the local level. And then the COVID

Prevention Network has this specific working group, which is building on its HIV trial experience, and that group is led by health equity experts. They've been very proactive in this area, and activities have been pretty widespread.

So specifically, they have stood up a series of expert panels with scientists from and working with priority populations. They have also stood up community working groups with research familiarity, and there are any number of stakeholder outreach events with national organizations, local townhalls, a specific faith-based organization outreach strategy, and grassroots organization. There's more work to be done there; there always is, and we're committed to doing it.

Generating and maintaining trust, this is the third priority both in the trials themselves and then the products that they've proved successful in the trials. We know this is critical because the vaccines will only be effective if that uptake is widespread.

You can have a fantastic vaccine, and, if no one takes it, it's not going to do much to end this pandemic.

There is a good deal of work to be done in this area. We know that a good portion of the U.S. public is skeptical of these vaccines and not jumping to take them once approved, at least at present. So what are we doing about it?

So first, maintaining safeguards for volunteers and for the study conduct, we are taking that very seriously as discussed earlier in the presentation. We're engaging directly with stakeholders from underserved minorities and that are hardest hit by the pandemic. And we're communicating the roles that entities like the NIH, like the VRBPAC, like regulatory bodies play in the careful evaluation and potential authorization of vaccines.

And importantly, we're committing to transparency. So the companies have made some real strides in this area, posting their final protocols, sharing enrollment data on an ongoing basis, including

enrollment by race/ethnicity. And the prompt sharing of results will also be a priority for us -- prompt sharing of full results.

Just to wrap up, if anyone is interested in participating in any of these trials, this website, preventcovid.org, will allow you to express your interest. You'll take a quick survey about your potential risk of infection. It's not committing you to the trial, but it's a way to raise your hand and say that you might be interested in volunteering. So thank you so much for the opportunity.

MR. KAWCZYNSKI: All right. Arnold? We have about just about two minutes. Are you there, Arnold?

DR. MONTO: I am here. Thank you so much for a very clear presentation. I think you've set the background for us for our later discussion this afternoon. I have only one question, and I'm just going to restrict myself to this one. I wrote you this one question. I noticed you are using a point estimate of efficacy of 60 percent. The guidance says 50

percent. Could you explain that?

DR. MARSTON: We use pretty closely to the guidance in most cases. We set a slightly higher bar than the guidance even had because of the urgency of the situation and because we wanted to make sure that this would have as great an impact as possible on the outbreak. Thanks.

DR. MONTO: Thank you and thanks for such a clear presentation again. I'd like to move on to introduce Dr. Robert Johnson. He is Director of Influenza and Emerging Infectious Disease Division at the Biomedical Advanced Development Research Authority, better known as BARDA. Dr. Johnson.

BARDA ACTIVITIES IN THE DEV OF VACCINES - COVID-19

DR. JOHNSON: Great. Good morning. As I was preparing for this presentation, I was struck by just how far we've come in development of vaccines, therapeutics, and diagnostics in such a short period of

time. It is really remarkable that less than ten months after identification of a new emerging infectious disease, we're at this meeting today being held on the general topic of advanced vaccine development and looking at potential pathways to authorization of licensure.

As mentioned, my name is Robert Johnson, and I'm the Director of the Influenza and Emerging Infectious Disease Division within BARDA within the Assistant Secretary for Preparedness and Response in HHS. I also serve as the vaccine product coordination team lead for Operation Warp Speed, or OWS, which as I am sure you all know is the Department of Health and Human Services and Department of Defense's joint effort to address the COVID-19 public health threat. Today, we'll provide you with a brief overview of the BARDA/OWS vaccine portfolio, specifically, how the portfolio was built, what does it look like today, and where are we going. But I first want to set the stage by providing the background on strategies and tools

that have been developed over the last decade that lay the framework for us to respond as rapidly as we have.

Apologies. I'm figuring out the -- ah, there you go. So as I mentioned, BARDA sits within the Assistant Secretary for Preparedness and Response. ASPR's mission is focused with a wide-ranging impact: save lives and protect Americans from 21st Century health security threats. This includes current activities such as providing support to those impacted by recent hurricanes, as well as numerous activities related to the COVID-19 pandemic response.

As part of this mission, BARDA supports development of medical countermeasures to detect, treat, and prevent a variety of threats, including pandemic influenza and emerging infectious diseases. This capability is built on core principles, which combined support a rapid response to emerging threats. The BARDA pandemics vaccines preparedness and response strategy is really based on three ideas. The first is acceleration of development.

How do we do that? One is looking at use of platform technologies which have previous experience. Related to that is doing activities in parallel. So it's not enough to simply have something that moves fast. We all know the standard development pathways, but the goal is how can we do things in parallel that we can accelerate that process?

Second is around manufacturing. Similar to what Hilary Marston mentioned earlier about a vaccine is only as good as it is people willing to uptake it, the vaccine is only as good also as it is the ability to produce it in sufficient numbers to get out and have an impact. So when we think about domestic manufacturing, really three things come into play. The first is, of course, you have to have the facilities in which to make the vaccine. The second is you need the raw materials and supplies to make the vaccine. And finally, you have to have a vaccine in a platform that's amenable to scaling up and scaling out, that you can make a lot of product in a short period of time,

and finally risk mitigation.

And what do we really mean by that? We really mean redundancy. We don't want to be putting all of our focus on just one technology or one approach or one manufacturing facility. We want to have multiples of each of these so that, if one does drop out, we have other candidates that are ready to come into place and move onto the next step.

It's great to have a strategy, but what are we really trying to accomplish with this strategy? So what you have here on this slide is a standard product development timeline where we look at things being done in sequence, typically one candidate at a time, and you have large scale manufacturing coming on fairly late in the process. And what we're really trying to do with the approach that I just described is, by relying on platform technologies, multiple candidates, and parallel the advance manufacturing, we're hoping to shrink the timeline such that we can accelerate the time to vaccine being ready and, at the same time, have

a vaccine ready to be shipped out.

Right. So everyone is aware that the COVID-19 outbreak is the third outbreak of a novel coronavirus since 2003. And while there are no licensed therapeutics or vaccines against these novel coronaviruses, as Hilary so eloquently outlined, several studies were conducted with these earlier outbreaks that gave important information from which to build from. Most importantly, from the clinical and non-clinical studies done with SARS and MERS, we knew that the coronavirus spike protein was immunogenic in clinical trials and could protect in non-critical studies. This information played a critical role in our ability to move forward quickly with vaccine development.

All right. So it specifically provided BARDA the key information to begin development of COVID-19 spike-based protein vaccines using platform technologies, including several that BARDA had previously supported with other infectious diseases.

So Hilary talked about the Moderna mRNA-based vaccine. Some of that earlier technology was done in collaboration with BARDA in the context of the Zika vaccine and so being able to lean -- to follow on with NIH's effort on that mRNA vaccine platform for COVID-19 and further supported advanced development of that product, similarly, bringing into play the R&D development of the R&D Janssen add 26 vaccines as well as the Sanofi/GSK influenza vaccine platforms.

So as work to develop vaccines and therapeutics against COVID-19 grew across multiple agencies and the scope of the effort really came into focus, it became readily apparent that a new structure was needed so these efforts to be accelerated by providing the necessary framework and capabilities to meet the goals of rapid MCM development. Further, we really needed a true end-to-end approach, unifying efforts across departments as well as across government, to allow seamless transition for every step of the process from development to vaccine

administration. So this resulted in formation of the Operation Warp Speed effort, which I referred to earlier.

So what exactly is Operation Warp Speed? Again, I provided a quick summary, but I wanted to touch briefly on how does this Operation Warp Speed really enhance the strategy I discussed earlier? And as I mentioned, it talks about the end-to-end solution, but it's really more than that. It adds resources and value to every step of the process.

So we have cross-departmental strategic guidance, oversight, and teamwork. This allows resources from multiple departments across the government to come together to be working on one task in parallel and together. It greatly enhances the logistical operational capabilities, as I'll discuss a little bit later.

We've heard already about the scope and the size of the clinical trials and the number of candidates that are being worked on. One of the things

we haven't talked as much about is the manufacturing requirements to be producing six vaccine candidates at such a large scale. So the logistical capability's requirements of setting up that supply chain is tremendous and requires great cooperation. Finally, it incorporates the expertise of DoD and DHHS to support the large rapidly enrolling clinical trials that Hilary talked about earlier.

So what exactly -- here you go -- and finally it puts all this effort under one roof. So I spent these last couple of minutes talking about the underlying strategy that formed the basis for product selection for the vaccine portfolio. And I've talked a little bit about the initial investments that were made in the vaccine candidates. So I want to now spend just a couple of minutes talking about where are we now, and then conclude with talking about where are we going.

So since May under the Operation Warp Speed effort, we've been able to do several activities that have greatly enhanced the portfolio, so those include

adding candidates, such as the Pfizer mRNA candidate as well as the Novavax recombinant protein-based candidate. Equally important, it allowed us to fully support large-scale manufacturing of these vaccines. And this is key in that it allows those vaccines, if they are proven to be successful, to be rolled out in a much more rapid pace than would normally occur if we were to follow the traditional product development timeline.

So what are the products in the current portfolio? Again, Hilary, I think, did a nice job providing an overview, and I don't want to repeat what she said. Six candidates -- a couple of things that I will touch on in regard to the initial strategy that was outlined. One thing is that the idea about having, from a risk mitigation perspective -- having multiple candidates on the same platform, so you'll see two candidates based on the mRNA platform, two based on the adenovirus platform, and two based on the recombinant protein platform.

Another important point that I would like to call your attention to is that these candidates, while they've been moving forward rapidly, have also hit each one of the steps that you would expect to see in a typical product development pathway. All of them have completed or have ongoing non-clinical studies looking at safety and effectiveness. They also have -- before they went into the Phase 3 clinical trials, they've also conducted Phase 1 and 2 clinical safety and immunogenicity studies, not just in the younger population but also specifically in that older population that will most likely benefit from a successful vaccine. And finally, as mentioned before, four of the six candidates are currently in the large Phase 3 clinical trials.

Hilary did a really nice job of providing an overview about how we conduct the Phase 3 clinical trials of the vaccine candidates in the OWS/BARDA portfolio, so I'm not going to repeat that. I put this slide up here for reference. But I will just quickly

point out and reinforce this idea that, while each protocol is -- the company is the -- the product developer is the sponsor for that, we do have -- there's an effort that allows this harmonization that is so important in terms of safety and effectiveness oversight.

So before I conclude, I want to touch briefly on where we sit in terms of manufacturing. So as I mentioned before, the capabilities, requirements, raw materials, facilities needed to manufacture six candidates at such a large scale is tremendous. When you think about the -- for example, something as simple as the supply chain, which for a normal product development pathway would take five to six years to really put in place and validate -- and we're looking to do that in the course of just a few months with six different candidates.

And this goes back to what I discussed earlier. One of the advantages of the Operation Warp Speed effort is that ability to align and get resources

across the government focused on one effort. And that effort is not just focused on the vaccine manufactures themselves but also making sure we have all of the supplies, equipment, and raw materials that are necessary to produce these vaccines.

So finally, I want to conclude. I thought Hilary's comments around the importance of uptake and confidence were really important, and they really hit on a key fact. And that's when we think, from the Operation Warp Speed as well as from the BARDA perspective, what are we looking to accomplish? So it really is hitting every one of those steps in the product development lifecycle, the manufacturing lifecycle, as well as the distribution and administration perspective because really the requirement is an end-to-end solution. We need to be able to do everything from the earliest stages of product development all the way to administration. So with that, I will thank you for your attention, and I'm happy to take any questions.

MR. KAWCZYNSKI: All right. Arnold, are you there?

DR. MONTO: I am here.

MR. KAWCZYNSKI: All right.

DR. MONTO: We have a few minutes for questions. I've stifled questions from the Committee. If anybody wants to ask a very short question, please raise their hands.

MR. KAWCZYNSKI: So we have the first one from Michael Kurilla.

DR. MONTO: Michael?

DR. KURILLA: Thank you. Robert, very nice overview. I was struck by the fact that the majority of candidates currently being supported are two dose vaccines. Was that just how there were many other factors that played into selection and you didn't have -- or was there few choices in terms of potential candidates that would be single dose? It would seem that for particularly a pandemic and an outbreak response that the single dose would be highly

desirable.

DR. JOHNSON: Yeah. I know. Thanks for that questions, Mike, and that's a great point. Before I answer that, just a little bit of background, from the BARDA and OWS perspective, you know, the portfolio is not fat, right? So we're always looking for candidates that will -- to potentially incorporate into the portfolio, and certainly a candidate with a single dose would be of great interest for the reasons that you mentioned. You know, I can say that when we were doing the initial evaluation, there wasn't one that really came across as being a single dose that we thought met all of those other criteria that were so important.

DR. MONTO: Next, we have a question from Dr. Notarangelo. Please unmute.

DR. NOTARANGELO: Good morning, Dr. Johnson. That was very clear. I have only one question. Can you tell us more about how many manufacturing facilities are involved for each company? Is it only one or more than one? And what is BARDA's position in

regard to what is mentioned in the October 2020 guidelines that do not require inspection of the manufacturing facilities in order to provide an emergency authorization, if appropriate? Thank you.

DR. JOHNSON: All right. So great question. So we are -- as I mentioned earlier in the talk risk mitigation is key for us, so we're always looking to have more than one facility capable to doing manufacturing. Of course, manufacturing isn't just one step. It just doesn't occur at one facility when we think end to end, but we are always trying to do everything that we can from a risk mitigation perspective to make sure that we have multiple facilities.

To get to your second one, I'll defer to FDA to respond. I won't speak for them in terms of their guidance document. I can say from our perspective in our interactions with our product developing partners, you know, quality is always paramount. And so this is something we are focused on heavily and spend a lot of

time and effort on regardless of when the regulatory authorities may come for or not.

DR. MONTO: Let's park that question until this afternoon. I want to call on a couple of more members. Dr. Chatterjee.

DR. CHATTERJEE: Yes. Thank you, and I think this question may be more for Dr. Marston, but perhaps you could take a stab at it, Dr. Johnson. Really, it's a two-part question with regard to the population that is being included in the trials right now. There have been media reports of inadequate numbers of patients from minority populations who are disproportionately affected by the pandemic. I'm also curious about future trials involving children, pregnant women, et cetera. My understanding is that, among the current trials, the only one that is enrolling children down to 12 is the Pfizer trial.

DR. JOHNSON: So I'll touch on both of those. I don't know if Hilary's able to jump in and actually will be able to add more detail. But, you know, in

terms of the diversity of enrollment, that's a key criterion for us. I think Hilary talked -- did really job of outlining the efforts that you're seeing to make sure that we meet those targets, and that is, I think as Hilary also pointed out, one of the key tenants that we have for the Operation Warp Speed effort, doing everything possible to make sure that those that are most impacted by COVID-19 are being enrolled and that we have good diversification across enrollment in the trial.

To get to your second question, correct, at this point, Pfizer is the only one that I'm aware of enrolling individuals as young as 12 years old in their clinical trial. There are discussions ongoing right now between the product developers and FDA about what enrollment of these younger populations as well as the other populations that you mentioned -- what that will look like and what we can do when.

DR. MONTO: Dr. Cohn.

CAPT. COHN: Apologies. I had the same

question as Dr. Chatterjee, so I don't have a question.

DR. MONTO: Okay. So finally, Dr. Wentworth.

DR. WENTWORTH: Thanks for that great presentation, Dr. Johnson. You mentioned a lot of these have already got data associated with virus neutralization tests, and, as you know, that can be a challenging process. And I was wondering if there's some activity going on to standardize that neutralization so that you better understand the level of neutralization from different platforms? Over.

DR. JOHNSON: That's a great plan and, Hilary -- I didn't touch on that in my presentation because I think Hilary did a nice job covering that. One of the tenants under the Operation Warp Speed effort is that we will use the standardized neutralizing assay across trials to get just to your point.

DR. MONTO: Okay. Thank you, Dr. Johnson. I think we have a break now. We're going to take a ten-minute break, which means we will reconvene at 11:50 Eastern.

[BREAK]

CDC PLANS FOR VACCINE SAFETY MONITORING & EVAL DURING EUA USE AND POST-LICENSURE

MR. KAWCZYNSKI: All right. So we're coming back. So all right. Welcome back. And we are going to be getting started for our second portion after break. Dr. Marks, would you like to kick us off here real quick? Go ahead and turn your camera on and take it away.

DR. MARKS: Okay. Thanks very much, everyone. I just want to take a moment. I'm Peter Marks, Director of the Center for Biologics Evaluation and Research. And just on behalf of the Center and FDA I just want to take a moment to thank a number of people, including all of those in the Office of Vaccine Research and Review who put a tremendous amount of effort into preparing for this Advisory Committee

meeting. I also need to greatly thank the Advisory Committee meeting staff and Dr. Atreya. They spent many, many hours getting ready for this.

This is an exceptionally well attended Advisory Committee meeting, more so than most. So a tremendous amount of preparation went into it. And I also want to greatly thank all of our advisors for participating today. We greatly appreciate all the input that you'll provide to us. So without that -- since it's a very busy day, I don't want to take any more time but thank you all and thanks to all our listeners today as well.

DR. MONTO: Thanks, Dr. Marks. We're going ahead now to the rest of the morning program, which basically looks at what happens after a vaccine starts to be used in terms of the monitoring safety and effectiveness and other important variables. And first, we're going to hear from the CDC from Dr. Shimabukuro and Dr. Schrag who are both going to tell us about the CDC plans for vaccine safety monitoring

and evaluation during future use and post-licensure.

DR. SHIMABUKURO: Hi, can you hear me okay?

MR. KAWCZYNSKI: Yes, we can. And please turn your camera on as well.

DR. SHIMABUKURO: I can't.

MR. KAWCZYNSKI: Oh, that's right. I will take care of that. Thank you.

DR. SHIMABUKURO: Hi, good morning, everyone, and I'll be covering CDC post-authorization/post-licensure safety monitoring of COVID-19 vaccines. By way of background, the U.S. government has a responsibility for public safety with respect to vaccines. Our monitoring is independent from manufacturers and covers all vaccines, and we maintain the largest, most robust, and most sophisticated safety monitoring systems available. And agencies collaborate on analyses.

CDC's Advisory Committee on Immunization Practices has established a COVID-19 Vaccine Safety Technical Subgroup. This subgroup has been advising

federal agencies on planning and preparation for monitoring, and it will independently review and evaluate safety data. And safety data will be regularly presented at public ACIP meetings.

This is a list of systems and topics I'll be covering. So I'll start out with the vaccine adverse event reporting system. VAERS is the national passive surveillance or spontaneous reporting system that is co-managed by CDC and FDA. VAERS can rapidly detect safety signals and can detect rare adverse events. As a spontaneous reporting system, the main limitation is generally we cannot assess causality from VAERS data alone. It is a hypothesis generating system and a signal detection system.

VAERS has all 320 million U.S. residents as a covered population for safety monitoring. In recent years, VAERS has received just over 50,000 reports per year. That comes out to about 1,000 reports per week.

Approaches to analyzing VAERS data include traditional methods like clinical review of individual

reports and aggregate report review. That's looking at large volumes of automated data. Statistical data mining methods detect disproportional reporting of specific vaccine adverse event combinations in the VAERS database.

VAERS traditionally has provided the initial data on the safety profile of new vaccines when they are introduced. For COVID, vaccine reports will be processed within one to five business days, depending on the seriousness of the report. CDC and FDA receive updated datasets daily, and data mining runs are planned to be conducted every one to two weeks.

So this is an example of the timeliness and responsiveness of VAERS going back to H1N1. This is the first published safety data that was published in the *MMWR*. The vaccines -- the H1N1 vaccines were licensed in mid-September 2009, did not become available until mid- to late October. The analytic period for this analysis was through November 24th, and the MMWR was published December 4th. That's less than

two months after the start of vaccination.

Moving on to the Vaccine Safety Datalink, the VSD is a collaboration between CDC and nine participating integrated healthcare organizations with data on over 12 million persons per year. VSD has information from electronic health records and administrative data all linked by study IDs with access to charts. Planned monitoring activities include near real-time sequential monitoring, what we call rapid cycle analysis. These are weekly analyses on accumulating data with adjustments for sequential testing. The outcomes in RCA are pre-specified.

Tree-temporal scan data mining looks for associations, and there's no limitation or restriction on the outcomes. These outcomes are not pre-specified. We also plan to monitor for vaccine mediated enhanced disease in VSD. VSD data are refreshed weekly, and there's an approximate two-week data lag from a patient encounter with the healthcare system until the data are in a refreshed database.

Moving on to the Clinical Immunization Safety Assessment Project, CISA is a collaboration between CDC and seven participating medical research centers. They assist U.S. healthcare providers with complex vaccine safety questions about their patients and conduct clinical research. And here's a map with the seven CISA sites.

Moving on to a new program called v-safe, v-safe is a new smartphone based active surveillance program for COVID-19 that uses text messaging to initiate web-based survey monitoring. It conducts electronic health checks on vaccine recipients daily for the first week post-vaccination and weekly thereafter until six weeks post-vaccination. It includes active telephone follow up through the VAERS program for people reporting a clinically important adverse event during any v-safe health check. And data will be available daily.

This is a schematic of v-safe. You see the bidirectional communication there between CDC and the

vaccine recipient. These are text messages with weblinks going to the recipient and the recipient transmitting information back to CDC on their post-vaccination experience. Clinically important adverse events include missing work, unable to do normal daily activities, and received medical care. If any of those are checked on any v-safe check in, VAERS will initiate active telephone follow up to contact the patient and take a VAERS report if appropriate.

Moving on to additional programs, so some other planned safety monitoring activities are safety monitoring in the Genesis Healthcare data. This is 350 long-term care facility sites in 25 states. And we're also planning to do facilitated VAERS reporting for healthcare workers and long-term care facility residents in CDC's National Healthcare Safety Network.

For planned activities for COVID-19 safety monitoring during pregnancy, we plan to identify and review all VAERS reports involving COVID-19 vaccination and pregnancy and adverse pregnancy outcomes. Vaccine

safety datalink studies are planned to evaluate safety in pregnancy, fetal death, and infant outcomes. And monitoring of vaccinated pregnant women and women who become pregnant after vaccination will occur in v-safe.

So in summary, CDC monitoring systems are capable of effectively monitoring COVID-19 vaccine safety, both under EUA and post-licensure. Analytic methods for VAERS and VSD have been validated through years of development and refinement. Data refresh and updates and timely, allowing for analyses in near real-time, and additional safety monitoring programs will contribute, especially early in the COVID-19 vaccination program. And I'm going to turn things over to my colleague Dr. Schrag.

DR. SCHRAG: Thank you. So just as questions will remain for safety after the Phase 3 trials, questions will also remain about vaccine efficacy. One thing we can be certain about is we will have efficacy information about the primary endpoints, which are symptomatic COVID-19 disease across the U.S. portfolio

of trials. But we may have limited and, in some instances, no information about some of the secondary endpoints. And I've pulled out just a subset relevant to public health here.

This would be particularly true in the instance of an early EUA because many of these secondary endpoints required longer time than the primary to accrue an event. Also, I just wanted to point out that for the infection endpoint, which is of interest because it relates to transmission, even if the trials run the full duration, there may be limited insights because of widely spaced blood draws and complications in interpreting serology. As we heard earlier, the trials have not focused to date on pregnant women and children, so for this talk I'm going to focus on adults.

So with this context, the need for post-authorization or licensure VE estimates is more important than usual, particularly if an EUA is issued early and we will have limited information. But it's

also needed for the usual reasons that real world protection can differ from efficacy under trial conditions. And most of the COVID-19 vaccine products in the U.S. portfolio require two dose regimens and varying cold chain conditions. So they could be challenging to implement.

Given this, we were able to conduct some internal consultations, as well as some consultations with external stakeholders and policymakers, including some of the members of the CDC's ACIP COVID-19 vaccine working group. And we really wanted to home in on the VE priorities that are of relevance to policymaking. And the results of these consultations are summarized in this table here.

Everything in the table is really a top priority, and those items I highlighted in yellow were just consistently mentioned and emphasized across our consultations as important. So we will need to go after product specific VE for an early phase of vaccination. When doses are limited, we will focus on

just assessing whether the vaccine is behaving as expected based on the trials.

But as we hit into a wider spread phase of use, we'll be interested in generating VE estimates against a range of outcomes and for key subpopulations and also looking at some regimen related questions that are what arise in real world conditions. And the reason why the infection and closely related transmission endpoint were emphasized by many of our stakeholders is because, from the policy standpoint, this is in some ways a fork in the road where policies for a vaccine known to protect against transmission can look very different from policies for vaccines that protect against severe disease but not transmission. And then as sufficient time has accrued, we will be interested in looking at duration of protection, comparative VE if there's more than one product, and also throughout the pandemic, and certainly after vaccine comes on the scene, we want to keep tracking the evolution of SARS-CoV-2.

So to develop the CDC VE portfolio, we used a few guiding principles. And just very briefly, we are trying in all of our efforts to facilitate rapid launch of our assessments. We appreciate the hunger and need for additional information. We want to harmonize and coordinate across platforms, U.S. government where possible, and even to combine similar platforms where possible for more robust VE estimates. And then we are including a diversity of methods within our portfolio analogous to what we heard earlier. This is a risk mitigation method because all of these have strengths and different limitations.

And all of our efforts will be observational in nature and face some challenges in common. Vaccination may correlate with risk of disease. COVID-19 epidemiology is dynamic, and our understanding of COVID-19 is also dynamic. And we're all hoping for more than one product available, but this could complicate estimation of product specific VE.

So now to really focus on our currently

planned portfolio for adults, in the left column you'll see the VE priorities that I emphasized earlier. And for each of these, we've tried to identify a prospective data collection approach. This can allow for participant interview. It can allow for, in some instances, specimen collection or chart review, so a very high-quality, rich dataset but often limited in sample size. So we've also tried in parallel to leverage the power of big data and to use electronic health record and claims databases and independent efforts to look at the VE priorities.

So looking at the prospective data collection column, most of our designs are leveraging the test negative design case-control method where we can. We're also pairing that with a conventional case-control approach using facility controls. And a few of the efforts in this column don't have a match with big data, so we think for the early phase of vaccination we're anticipating that healthcare workers may be one of the groups that will be earlier recipients of

vaccine. And we've designed a prospective platform but don't have a big data counterpart.

Similarly, for the key VE against infection or transmission we have launched already a prospective longitudinal cohort aiming to include about 5,000 healthcare and frontline workers to be ready for the early rollout of vaccine. And we're in planning stages of a general community or a household VE cohort for the wider spread phase. Otherwise, in the prospective column we're leveraging hospital and ICU enriched platforms to look at severe disease, outpatient platforms for non-severe, and we also have a test negative design study in the American Indian/Alaska Native population.

So on the big data side, what this represents is a coordinated effort across the U.S. government. The key players will be CDC, VA, FDA, CMS, and we're also exploring collaboration with IHS. Most of these will use a retrospective cohort design, but other methods may be appropriate and used. And for the

elderly, we think the CMS dataset is probably the most powerful, even more powerful potentially than our prospective design. And FDA will be leading that effort.

So we have a few additional analyses also planned. These may not all generate VE but will provide important context. We're hoping if the state immunization registries are capturing vaccination administration well that we may be able to use the screening method for snapshots of product specific VE. We're interested in ecologic analyses and comparisons of expected vaccine impact based on modeling with observed impact. We're designing studies in pregnant women and children, and we are leveraging the SPHERES project, which was launched in the spring, as an open genomics consortium to try to track any changes in the virus over time.

So just to conclude, many questions of importance will remain after EUA or licensure with regards to effectiveness. Our portfolio leverages

multiple platforms, data sources, and methods and will continue to evolve as more information from the trials becomes available. And I just wanted to acknowledge all the platforms that we will leverage. Thank you.

MR. KAWCZYNSKI: Arnold?

DR. MONTO: Thank you.

MR. KAWCZYNSKI: We have a -- go ahead. Take it away.

DR. MONTO: Right. Thank you, both. We have time for a couple of critical questions. Dr. Gans?

DR. ALTMAN-GANS: Thank you. Thank you very much. This question might be directed at Dr. Shimabukuro. I really had a question about the expansion mostly of the VSD. I mean, a number of platforms were thrown up in terms of how we're going to mine the data, but there's some real key geographic sites. As robust as VSD is -- and it's really been an incredible resource to look for signals that may, as you indicate, by hypothesis come from VAERS, but I'm worried that it doesn't fully capture the geography of

this disease. And I also wonder about collaborations with our colleagues globally because we're going to be learning a lot, I think, together on this.

DR. SHIMABUKURO: This is Tom. You're correct that the VSD sites tend to be concentrated on the West Coast and are heavy on the California Kaiser programs. We've done some looks at the VSD data, and although it's geographically concentrated, it is fairly representative of the racial and ethnic demographics of the United States as a whole. I think Dr. Anderson in a future call will be talking about some of the other systems, so the CDC and FDA have complimentary systems. And we collaborate and cooperate on our monitoring.

We also are working with global partners on trying to harmonize some of our methods and to leverage systems globally in other countries and with attempts to combine data to get a better overall picture of safety monitoring. Did you have another question? I'm sorry. Did you have another question? Is that your -- part two of that question? I just hung up on part one.

DR. ALTMAN-GANS: No, that's great. Thank you very much.

DR. MONTO: Let's go on to Dr. Meissner, and we're going to continue the presentations after that because we may want to have a more general discussion of the various post-marketing surveillance systems afterwards if we have the time. Dr. Meissner?

DR. MEISSNER: Thank you and thanks both presenters this morning. So I want to just clarify, Dr. Shimabukuro, the VAERS, VSD, and CISA will apply to a vaccine that's licensed under an EUA?

DR. SHIMABUKURO: Yes, we plan to conduct post-authorization monitoring using our established systems and some of these new systems during the EUA period and during the post-licensure period when the vaccine's become licensed.

DR. MEISSNER: And will every subject receive a cellphone? Because that could be a huge number of people.

DR. SHIMABUKURO: Our goal is to enroll as

many people as possible through the v-safe program. I didn't really have time to get into the specifics of enrollment, but initially people will be able to enroll either by going to a URL or scannable QR code and register and begin to get text messaging. We plan to use VAERS to follow up on what we call clinically important or medically important adverse events. So essentially, it's leveraging the VAERS system to help us conduct active surveillance in v-safe.

DR. MEISSNER: Thank you.

DR. MONTO: Okay. Thank you both very much. We're going to move back to FDA now, and we're going to hear from Steven Anderson, the Director of the Office of Biostatistics and Epidemiology in CBER on the CBER surveillance systems post-marketing.

CBER SURVEILLANCE SYSTEMS/POST-MARKETING

DR. ANDERSON: So Mike, I just wanted to say I'm having trouble. The screen is frozen, so I think

I'm going to have to do this as an audio presentation.

MR. KAWCZYNSKI: You're there, but I have your photo. So I'll throw your photo up there for you, sir.

DR. ANDERSON: Somebody's going to have to advance slides.

MR. KAWCZYNSKI: Sure. Not a problem.

DR. ANDERSON: All right. So hi, my name is Steve Anderson. I'm Director for the Office of Biostatistics and Epidemiology. And today, I'm going to talk about CBER's plans for monitoring COVID-19 vaccine safety and effectiveness. So FDA's approach for safety is really a safety throughout the lifecycle approach for vaccines and for its regulated products. And that includes pre-licensure as well as post-licensure space.

And so moving to the pre-licensure space, the safety data comes in through the various phases of the studies that are conducted, evaluated quite thoroughly by the review teams. As part of that, there's also a pharmacovigilance planning process. So manufacturers,

when we get to the biological license application process, submit plans. They would also do this under an emergency use authorization as well. And those plans really outline the safety questions or issues or concerns that arose and then suggest plans for dealing with those specific safety questions or concerns that arose in the process of studying the vaccine.

So what a sponsor may do is suggest doing a post-licensure or a post-market commitment, and that might include various types of studies, registries. And those might be for general safety. So if a vaccine's being given to women of childbearing years, which these COVID vaccines will, we might suggest that -- and the sponsor may suggest that they might do, for instance, a registry to make sure that that kind of general question is answered.

We might also impose or discuss -- they may suggest doing a pre-licensure or post-market requirement, or PMR. And that might be something such as another clinical study, an epidemiological or

observational type study, registries. And the difference between this and a post-market commitment is this is a required study to study a specific safety signal that arises. So for instance, if they get a potential safety signal for something like Guillain-Barre syndrome, then they might need to do PMR.

MR. KAWCZYNSKI: Dr. Anderson?

DR. ANDERSON: The other thing is -- yes?

MR. KAWCZYNSKI: Dr. Anderson, real quick, first off, if you don't mind, you can log out and log back into Adobe real quick so that way you can be back up. But also, what slide are you on so I can make sure we're on the right slide?

DR. ANDERSON: I'm on the second slide.

MR. KAWCZYNSKI: Okay. If you'd like, you can log out and log back into Adobe.

DR. ANDERSON: I don't want to lose the audio connection is the problem.

MR. KAWCZYNSKI: You won't. You won't. You can keep going. Just make sure you tell us to advance

slide if you're going to.

DR. ANDERSON: All right. So and then finally the baseline is sort of routine pharmacovigilance, which includes anything from passive surveillance to review of safety literature, available studies, et cetera. So the next slide, this just gives an overview of post-licensure programs that we have. So passive surveillance is one approach that we use, and Tom has talked about VAERS. And then we'll talk about the active surveillance monitoring programs that we have.

So I'm just basically going to talk first about the passive surveillance at a high level. So Tom has already really covered a fair amount of this. I'm stealing his slide. So VAERS is this program that's co-managed by CDC and FDA. I'm sorry. This is slide 6. I keep on forgetting to tell you that. So the slide header is VAERS and FDA CBER effort. So the CDC presentation covered VAERS, so I'm just going to provide an overview of FDA efforts.

FDA and CDC, I just want to mention that we

have weekly and biweekly coordination meetings on VAERS and then our pharmacovigilance activities right now going on for COVID-19 vaccines. That includes the CBER front -- CBER Office of Biostatistics staff in the front office, as well as the Division of Epidemiology, CDC's Immunization Safety Office, and others at CDC. I want to mention that our Division of Epidemiology physicians will be reviewing the serious adverse event reports that come into the vaccines. They review individual reports, actually very closely scrutinize death reports, conduct aggregate analyses, and then case-series and a variety of other types of analyses. And I think as Tom mentioned, we're going to be using statistical data mining methods to identify if there's any, again, potential safety signals that pop up or are more frequently reported.

Next I want to -- slide 7 -- I wanted to talk about our active surveillance monitoring program. Going to slide 8, the next slide is talking about FDA's vaccine safety monitoring programs and legislative

authorizations. I just wanted to mention that there is legislative mandates for these programs that we're going to be talking about. The first one is really around the FDA Amendments Act. That directed FDA to develop what essentially is the Sentinel system, and the BEST initiative really is part of the Sentinel initiative. And the mandate by 2012 was to cover more than 100 million persons.

So I'm going to show you some big data systems, and just keep an eye on that 100 million number because that's the number that we shoot for when we're doing these types of safety evaluations. And then the Prescription Drug User Fee Act, the last iteration was 2017, just a discussion between FDA and industry on priority areas. And the Sentinel system and BEST received funding through this User Fee Act to fund activities.

I wanted to touch on data considerations because I think those are important for vaccines. What we're looking for in data systems are really rapid data

access for near real-time surveillance. Large databases -- this is slide 9, by the way, sorry. Large databases of tens of millions of patients for evaluating rare serious adverse events, data representing integrated care spectrum, meaning outpatient to inpatient -- and that means -- vaccines are largely given in in outpatient setting or a physician's office or clinics. But what we also want to be able to capture is, if a patient comes into an emergency department or the hospital with a serious adverse event, you want to be able to capture the entire spectrum of those visits in the patient records and have systems to do that. You want high quality data because it's very important to get -- if you identify a safety signal, very important to adjudicate that and get that validated properly. You want data with significant clinical details and preferably access to medical charts.

So moving on the slide 10, just a brief overview of the Biologics Effectiveness and Safety

System. It includes several partners. The first three are sort of contractors. We have academic partners. We have large insurers that are part of the program and mention that we also have point of care facilities and healthcare providers such as MedStar represented and, again, across the entire setting of healthcare spectrum.

Slide 11 talks about claims data sources. And just to remind people that claims are obviously the billing data and administrative types of information that are used to send patients -- to bill patients for services received in a care visit. And you can see off to the right that many of these systems are in the tens of millions of patients that they cover. The last three or four are ones that just newly came on board with the BEST program, so we're going to be engaging those for use for COVID evaluation -- COVID-19 vaccine evaluation.

I wanted to talk about electronic health record data sources too, and many times the electronic

health records provide a richer source of data than the claims data. So as you look over to the right, you can see the numbers vary from 1.5 million upwards to 105 million for Optum EHR system. So we have a lot of coverage with these potential data systems. And then an important thing also to consider is they have strengths and limitations, which I'll talk about in a minute.

I wanted then before I do that, though, to talk about the Center for Medicare and Medicaid Services data. FDA's had an ongoing partnership with CMS since 2002 to look at vaccine safety and effectiveness. The data cover a very large population -- I'm sorry. This is slide 13 -- and cover approximately 55 million elderly persons for 65 years of age or older. It represents a variety of healthcare settings that we're often looking for. And then they're claims data, but we can get access to medical charts for adjudication of adverse events. So this has been a powerful system that you'll see in a minute for

many of the studies that we've been doing.

I just wanted to talk a bit about limitations of these data systems because I've thrown a lot of numbers and data systems at you. And I'll just say not all claims and EHR systems can be used to address a vaccine safety or effectiveness regulatory question. So as you're looking at these systems, just remember each one has its limitations so, for instance, the populations they cover.

So for instance, Medicare covers the elderly population, but it doesn't give us as much information on individuals less than 65 years of age. It may not cover the healthcare setting of interest. It may just cover, let's say, hospitalizations and so on and so forth. And it may not actually cover the exposures and the outcomes of interest to us either. We may not be able to capture vaccines that we would like and then the adverse outcomes that we'd like to see.

Slide 15, I'm going to talk a bit about safety surveillance planning that we're doing. So like

CDC, we're planning to do near real-time surveillance or rapid cycle analysis. We're planning on at this time monitoring 10 to 20 safety outcomes of interest to be determined sort of on a variety of factors. One is on the pre-market review of sponsor safety data submitted to FDA. So we'll be looking very closely at that data and especially the Phase 3 safety data to identify potential safety questions of interest for us to study with our rapid cycle analyses.

We're also going to be looking at the literature and regulatory experience with these vaccines and any experience or knowledge gained from looking at the vaccine platforms and their use in past vaccines and other relevant data. We're also going to be coordinating all of this work with our federal partners, which I'll talk about at the end of the presentation. So our 10 to 20 -- list of 10 to 20 should largely be the same as CDC's and other federal partners. It's the plan.

And I will say for our plans, we plan on using

CMS data for COVID-19 vaccine rapid cycle analysis as sort of our first set of surveillance that we're going to be doing for any new COVID-19 vaccine. Tom had this list of possible adverse event outcomes of interest. I won't dwell on this. He had them at the end of his presentation. So we'll be coordinating which of these and others that we might be using in our rapid cycle analyses, but it gives you a feel for the types of events.

I'm sorry. This is Slide 17. FDA's experience with near real-time surveillance, so we have considerable experience doing near real-time surveillance. So we've conducted surveillance for the annual influenza vaccine and Guillain-Barre Syndrome since 2007. And then we're supporting confirmation of some of CDC's work with their rapid cycle analysis of safety, and we've done that in the past for the seasonal influenza vaccine work that they've done and Shingrix vaccine as examples. We've also done rapid cycle analysis type work or rapid surveillance in

Sentinel doing near real-time surveillance in the 2017 and '18 seasonal influenza vaccine looking at six health outcomes of interest.

So the question I think then becomes, once we get these signals, how do we adjudicate them. So another capacity that we've built is really the ability to conduct epidemiological analyses to really look at any of these signals that we get from sort of the screening methods that we're using in the near real-time surveillance. And there's also TreeScan and other signal detection methods where we'll need to adjudicate signals. So we've got that capacity with these large databases to do that. So we can do some rapid queries and small epidemiological studies. We're prepared to do those. But we can also do larger sort of protocol-based studies that might include sort of approaches such as self-controlled risk intervals, cohorts, or case-control type analyses.

The next slide is Slide 19. I wanted to talk about our effectiveness work. I won't go into the

level of detail that Stephanie did just for the sake of time. But there may be limited information on effectiveness at the time of licensure or authorization of these vaccines. And I just want to remind people that manufacturers have a part in this as well. They're doing the pharmacovigilance plan for safety. They'll also be making proposals for studies that they might conduct or vaccine effectiveness post-licensure studies.

But FDA may conduct studies, too, along with CDC on vaccine effectiveness. So we're talking as well along the lines of what CDC is: general effectiveness studies, including subpopulations of interest like patients with co-morbidities, elderly, elderly in long term care facilities and the like. We're also interested in duration of protection studies, so those are on the radar screen for us. And I will just say that this is all being done in regular coordination with CDC through monthly and bimonthly meetings just to make sure there's no redundancy in the work that each

of us are doing.

The next slide is Slide 20. I just wanted to talk about our vaccine effectiveness experience. We have extensive experience with the data and methods to conduct this kind of work. We've produced several vaccine effectiveness and relative vaccine effectiveness studies for influenza and zoster vaccines and then conducted a duration of effectiveness analysis for Zostavax. So again, this work goes back probably eight to ten years that we've been doing this type of work.

The other thing is we've been using the CMS data to understand and do some foundational work understanding COVID-19 diagnosis and the factors for reporting it in these data systems. So that work has been -- at least initial work has been of characterizing, and sort of doing the natural history type studies of patients is submitted for publication. And I just wanted to remind people that just in the past we have significant publication records in this

area, congressional testimony, and the like.

Moving to the next slide, I just wanted to talk about transparency considerations. So we're developing master protocols both for safety and effectiveness outcomes that we want to study. We'll be posting the draft protocols out for public comment, and that's generally about a two-week period. We'll consider those comments and update the protocol as needed and then post final protocols and final study reports, just again to keep the public informed and stakeholders of the work we're doing. That'll be posted on the BESTinitiative.org website. And then I just wanted to reiterate I think the --

MR. KAWCZYNSKI: Dr. Anderson?

DR. ANDERSON: Yes?

MR. KAWCZYNSKI: We have about two more minutes.

DR. ANDERSON: Okay. So I just wanted to emphasis this is a government-wide effort. We've been working closely with CDC, CMS, VA, and then others are

involved in the work as well. And I just wanted to remind you that that includes sort of regular meetings, the idea of sharing planned protocols and discussions of safety and effectiveness outcomes of joint interest to us, and we're coordinating those plans for near real-time surveillance with our sister agencies as well. And with that, I just wanted to end with acknowledgements to my CBER colleagues but also the many colleagues from other government agencies and our contracting partners for the work that they do. And I will stop there. Thank you so much.

MR. KAWCZYNSKI: All right. Arnold?

DR. MONTO: Thank you, Dr. Anderson. I'm going to -- I think we have time. Well, we really don't have time, but if there are two burning questions, please raise your hands. Dr. Gans?

DR. ALTMAN-GANS: Thank you. Thank you for that. I had a couple of questions. Just one of them is really about how we're keeping the data mining agnostic so we can really actually find potential

signals that weren't predetermined. I know you spoke about that, but I really just want to make sure that there is an agnostic approach to that. I have a bunch of questions about the databases. You had mentioned Sentinel. You had mentioned BEST, and I just want to make sure that those are going to be used since they were pretty -- not BEST, but Sentinel was really prominent in the H1N1. And that was an important system that was being used.

BEST is hospitalizations, but I'm wondering if that's going to be expanded to this use. And then my last question is just about I didn't see -- I don't know in all the data systems are you utilizing the EPIC system that's used in most children's hospitals and should be in place for when we hopefully extend these to children? Thank you.

DR. ANDERSON: Yes, all right. So there's a lot to unpack there. We are trying to keep the data mining signals agnostic. I think I'd point you to other experts at CBER that can probably talk to that

better than I can. The goal is to use as many of these data systems and continue to improve and sort of expand BEST so that we can continue to do this type of work. Right now, we're in this sort of consolidation phase where we're trying to understand each of the datasets that we are using and their strengths and limitations for doing this type of work.

And then you're third question was really around children. So we've engaged PEDSnet in this work, so we're in the process of onboarding them. And that's a network of about, I think, eight to ten different pediatric children's hospitals and networks that we'd like to bring onboard. But they're certainly part of this whole effort, and we're thinking that, especially in later efforts for safety and effectiveness surveillance, they'll become an important part of this work.

DR. MONTO: Dr. Nelson?

DR. NELSON: Good afternoon. Great presentation. Thank you for that important data. I

have two quick ones. In your list of EHRs that you're using or looking at to consider for real-time monitoring -- perhaps I missed it -- I didn't see the DOD or the VA electronic medical records. And those closed health systems with longitudinal follow up with those patients I think would be an important resource, and I'm sure it's already probably on your plate. My other question --

DR. ANDERSON: Yeah. Oh, go ahead.

DR. NELSON: The other one, which was more substantial, was I wondered if you'd comment on the impact of the lag of data acquisition for some of these paths of reporting systems and CMS in general with only 90 percent of CMS claims getting in within a three-month period. Normally okay, but under these circumstances and perhaps with the EUAs for these vaccines, more real-time data might be needed. Thanks.

DR. ANDERSON: Well, we have preferred access to CMS data, so I think the data stream there for us -- we can get weekly or almost regular updated feeds from

them every couple of days if we want. And it starts with unadjudicated data, but then, as the adjudicated data is added, the data all get updated. So this isn't a research database. This is actually access to live insurance data stream. So we sort of have a unique access as a government agency to the CMS data.

But you're right. Lag is a huge concern to us, so we try to keep it under a month or two for many of the systems, especially the claim systems. But the claim systems generally go out three or four months of lag. So that is a challenge, but the EHR systems are a bit quicker. So we're trying to build more EHR capacity, and those can be in a matter of days to a week or two for the lag.

DR. MONTO: Okay. Thank you very much. We're going to hear next about the operational aspects of COVID-19 vaccine distribution and tracking from Captain Janell Routh from the Division of Viral Diseases at the CDC. Dr. Routh?

OPERATIONAL ASPECTS OF COVID-19 VACC DIST & TRACKING

DR. ROUTH: All right. Thank you all very much. I'm really pleased to be here today. I'm a pediatrician by training and a medical officer in the National Center for Immunization and Respiratory Diseases. Today, I will lay out the implementation plans that we've been developing here in the vaccine task force in conjunction with our partners at Operation Warp Speed.

So COVID-19 vaccine continues to be a complex and ever evolving landscape. Before focusing on what we're planning for, I want to acknowledge the major challenges involved in rolling out a vaccine product as complex as the ones under investigation, as my other colleagues have done today. There are products that will likely have one or two dose series. Products may not be interchangeable.

We do predict that vaccine efficacy and adverse event profiles will be different in different

populations, adding to the complexity of getting the right vaccine to the right person. Cold-chain requirements will vary and could be complicated by an ultracold product or multiple products all requiring different specifications. We don't know yet how children and pregnant women will be included or recommended for vaccination.

Vaccine administration will be challenged by the need to maintain social distance in conjunction with infection control guidance. And last but not least, communication and education around these vaccines will have to be done carefully in order not to jeopardize our long-standing vaccination program. We know that trust and hesitancy are issues, and it's important to get in front with our messages that are crafted by the data and scientific processes that CDC adheres to.

As has been discussed, rollout of vaccine is undoubtedly a phased approach, not to be confused with the phases of the clinical trials. We've focused our

planning efforts around three phases -- those first weeks of limited doses where the intent will be to get vaccine out to groups likely to be selected for early access, such as healthcare providers, through tightly focused administration. Next is the second phase where increasing doses allows for the expansion of vaccination efforts beyond these initial populations and into broader settings, with an emphasis on populations that may require special consideration to ensure distribution and access. And finally, we do reach a point where supply outweighs demand, and the key is to make sure that access is available for anybody who wants to be vaccinated.

Vaccine implementation done right has many moving pieces, from prioritization and allocation to distribution, administration, and tracking safety, effectiveness, and uptake, especially around that second dose. It's important to remember that the success of these pieces is driven by good communication and stakeholder guidance, as well as regulatory

considerations that build trust and confidence in the vaccine. What I'd like to do now is to walk you through the key components of implementation and what we are doing to ensure these pieces fit together into a seamless rollout.

The public health impact of vaccination program relies on the rapid, efficient, and high uptake of the complete vaccine series with a focus on those at increased risk for severe illness. I do want to emphasize that we are thinking through carefully critical populations to ensure access to vaccine in earlier phases. Those selected to receive the first allocation of vaccine may be populations who provide critical infrastructure services, like healthcare providers, and other essential workers, like emergency management personnel.

But while we focus on that first allocation, it's also important to begin planning for populations to be prioritized in the next phases, which will follow quickly. These are persons at increased risk for

severe illness, like older adults and those with underlying medical conditions; those who have increased risk of infection, such as persons living or working in congregate settings; and those persons with limited access to vaccination. Right now, we're asking jurisdictions to identify and enumerate these critical populations and making sure that they reinforce partnerships with those trusted community organizations so that method for rapid information sharing will exist once vaccine or vaccines are available to distribute.

So here's an overview of the vaccine distribution concept down to the administration sites. Vaccine will flow from the manufacturers contracted by Operation Warp Speed either to the distributor or, for a vaccine requiring ultracold chain maintenance, direct from the manufacturer to site of administration. At the same time, kits containing ancillary supplies, such as syringes, alcohol pads, some limited PPE, and adjuvant or diluents required will be packaged and shipped to the distributor depot. Vaccine and kits

will be ordered and shipped separately to arrive either from the distributor or from that regional depot. Jurisdictions will order against a defined allocation of vaccine as it becomes available and will direct it to a variety of different administration sites, which will likely depend on that phased rollout. As vaccine becomes more available, we will start bringing in commercial partners, like pharmacies, who will be given direct allocations to expand that footprint of vaccination sites across the country.

One key piece of vaccine administration is making sure we have a sufficient number of providers who can administer vaccine, particularly in the early phases when we want to reach those critical populations. Onboarding and training of providers is vital to ensure the success of this vaccination program. There are multiple unique considerations for COVID vaccine administration that we are taking into account when thinking through vaccination clinic setup and throughput.

Regardless of whether that clinic is a mass vaccination activity, a drive-through operation, or housed in a health center, these considerations do apply. First is maintaining social distance and infection control guidance for a vaccine clinic management. This means spacing out persons and having an appointment scheduling process to avoid overcrowding. Second is storage and handling capacity of the frozen products. We're not recommending at this time that hospitals or clinics purchase ultracold equipment. If an ultracold product is granted an authorization to administer, it will come in its own shipping container that is able to maintain that cold-chain for a period of time to administer vaccine doses.

Security may be a concern at some clinics and making sure that the clinic staff and patrons are safe is part of that key clinic design. And finally, clinics must have the ability to have time to speak with patients and provide them the information required under an EUA. This step is critical because, for some

vaccines, patients will need to come back for that second dose. A good experience with time to answer questions and counsel on vaccine safety will go a long way to ensuring that return visit. Sorry, I missed that slide. Apologies.

So CDC and our Operation Warp Speed partners have developed an end to end data structure to monitor and track the distribution, administration, uptake, and demand for vaccine. Starting on the right of the slide, providers use partner systems or jurisdiction immunization information systems to input orders against a defined allocation into CDC's VTRekS system, which transmit the orders to the distributor. Administration and inventory is tracked on the provider side, as well as the distributor. And data flow to CDC and Operation Warp Speed for analysis in order to have end to end visibility on each dose.

We are leveraging existing well-proven immunization systems through our jurisdictional partners to conduct the COVID vaccination program.

Jurisdictions are well-positioned to execute this program because they know their populations, their enumerations, and where they live. They know where their at-risk populations can be found and who those key stakeholders are. They know how to reach those hard to reach populations through established channels, and they know where their providers practice.

They also have existing relationships with hospitals that they can leverage to start thinking through that Phase 1 administration. How to order, track, and report on vaccine administration and adverse events is something that jurisdictions are well aware of, and they also know how to run vaccination clinics, manage cold chains, store, and handle vaccines. And they know how to get vaccine or other product out in an emergency or outbreak situation. And finally, they know how to execute large scale vaccination to control and prevent illness.

We released the interim playbook on jurisdictional operations on September 16th to assist

jurisdictions in their planning efforts. It contains 15 sections on all aspects of vaccine planning specific for COVID-19. This is an iterative document, and it will be updated as new information is learned.

We are currently providing regional technical assistance to support jurisdictional planning, and our teams are doing a multitude of things to make sure that planning is going smoothly. They're collecting and analyzing metrics on capacity, providing direct technical assistance, including on the ground assistance in some states. And they're helping to facilitate cross-regional collaboration for best practice sharing. Teams are training jurisdictions on these new data systems we're bringing on board, including the Operation Warp Speed Tiberius system and CDC's data dashboard. Right now, we're currently in the process of reviewing those jurisdictional plans. And once we do we'll move forward with providing continued technical assistance once vaccine is available to make sure that jurisdictions have a smooth

rollout.

So to distribute and administer COVID vaccine, we need to leverage the help of many partners to ensure the success of this really unprecedented effort. We are leveraging public health expertise from the whole of the United States government, as Dr. Johnson outlined in his presentation. And we're also valuing contributions from private partners.

Pharmacies can help increase access to vaccines. Almost 90 percent of Americans live within a ten-mile radius of a pharmacy, plotted here on the map with both big chain stores shown by the red dots and the independent pharmacies in blue. This provides a massive footprint to get vaccine out to the public, particularly in those rural communities.

We see pharmacies existing across all stages of vaccine rollout. They'll be assisting in Phase 1 to ensure targeted vaccination of long-term care facility staff, as well as other essential workers and persons at higher risk for severe COVID-19, such as older

adults. In Phase 2, they'll help expand access to the general public via their large networks.

Jurisdictional vaccination plans were return on October 16th to CDC, and as I mentioned we are in the process of reviewing them right now. All 64 jurisdictions did submit a plan for review. Our next steps are to ensure that at the jurisdictional level they continue to work with commercial partners and our federal entities who may receive direct allocation to expand access, particularly in Phases 2 and 3. We ask that they enumerate their critical populations who may be selected for early vaccine allocation or, again, require that special consideration around distribution and access.

We're asking that they proceed with the collection of vaccine provider agreements to make sure those providers are onboarded, including providers that serve those critical or early access populations. We want to make sure that they have their state data systems connected and the processes to monitor vaccine

distribution, uptake, demand, and wastage are all intact. And then finally, we're really asking that they begin engaging with the community stakeholders to address the issues around vaccine hesitancy.

I can't talk about distribution without addressing concerns about vaccination. We know that vaccine hesitancy is an issue and that we need to rise to the challenge to achieve high coverage, both with seasonal influenza and also COVID-19 vaccines when available. We know that certain racial and ethnic minorities have consistently lower vaccination coverage than others, shown here on the graph of influenza vaccine coverage by season. We need novel and robust strategies to increase vaccine uptake, both for seasonal flu and for COVID-19 vaccine.

Focus groups conducted this summer by CDC show that participants were open to getting vaccinated eventually but were hesitant to receive it when first available. Concerns included safety, side effects, vaccine effectiveness, and if there was sufficient

testing in their group, meaning their age group or race and ethnicity. Participants wanted more information on vaccine products and said they would take a "wait and see" approach before making a final decision. And most said that a six-month period would be a reasonable timeframe to sort of wait and see.

Our Vaccinate with Confidence campaign that was developed at CDC is now being used to reinforce confidence in COVID-19 vaccine. We are using this framework as a starting point for communications around COVID-19, taking into account the critical factors raised by our focus groups. Using this framework, we will work to reinforce trust by sharing clear and accurate COVID vaccine information.

We're working to get information out to our website so that effective resources are available to providers to promote confidence both among healthcare personnel. We want them to get vaccinated and also to recommend they vaccinate their patients. And finally, we are working through our community partners to

collaborate with trusted messengers in these communities that are at increased risk for COVID outbreaks and also for disease complications.

Activities to support the Vaccinate with Confidence strategy for COVID-19 include gaining insights into vaccine hesitancy through ongoing data collection, continuing to develop strategy around the three key components that I mentioned in the last slide, developing a rapid community assessment guide, and providing ongoing support to the jurisdictions as they address hesitancy in their communities. CDC has a vaccine website that is now live. It has web content on a separate web page, but it sits underneath our larger COVID website. And we will continue to update this as new information arrives.

We also have a new ACIP web page that describes the recommendation process to help build confidence that we are ensuring safe and effective vaccine delivery. And with that, thank you very much. I'm very happy to take questions.

MR. KAWCZYNSKI: All right, Arnold. We have a few questions that did pop up.

DR. MONTO: Thank you, Dr. Routh. I have a question about procedures. If two vaccines are available at the same time and both require two doses, how do you keep it straight at the clinical sites which vaccine the person has received the previous time?

DR. ROUTH: Right. So an excellent question. We are going to have both electronic systems and also a failsafe backup system to ensure that we get that correct second dose to the right person. We are going to be having systems that do track and help people administer the correct second dose.

In every ancillary kit that is shipped with a vaccine allocation, there will be a vaccine card that is filled out and given to the vaccine recipients. We are asking that they keep and return that card when they come back for their second dose. That card will contain information about the vaccine that they did receive and the timing in order to ensure that they get

that appropriate second dose.

DR. MONTO: Thank you. I'm going to continue with questions. I just want to let everybody know that we will be eating into our lunchtime because we're going to return at 1:30 Eastern. So Dr. Pergam, you're next.

DR. PERGAM: Thanks for that great presentation. It was an excellent review of everything that's at stake. I'm curious. One of the populations that is also at risk for development of complications are immune-suppressed population. It makes up about 4 percent of the United States, and it's not been discussed in any of the reviews about how this population is going to be addressed. And one question I would ask is, is there any efforts to prioritize families in close contact with those individuals since they would most likely not be available for the vaccine in the early phases?

DR. ROUTH: Thank you for that question. I know that we are thinking through multiple different

critical populations in order to think through some of the access issues that will arise around vaccination of these populations. And I think that is a critical one. I know in many communities, not just with immunocompromised populations but with older adults, their younger children are often the caregivers.

And so I think you're absolutely right. We do need to give special consideration in some of those communities for caregivers. We've been focused a lot on healthcare providers, but we know that those caregivers are also healthcare providers in the homes of those immunocompromised patients and others at increased risk for severe outcomes from COVID. So I appreciate the question. I think we will definitely be thinking that through as we move forward with our prioritization scheme.

DR. MONTO: Dr. Chatterjee?

DR. CHATTERJEE: So I have a two-part question, Dr. Routh. The first is with regard to mandating these vaccines, either for healthcare

professionals or emergency management personnel. Has that mechanism been discussed, and what is the plan if so? And then the second part is, once the vaccines are deployed and appropriate numbers of doses have been administered, does the CDC have any plans in place to discuss the use of PPEs and other mitigation measures for those who are vaccinated?

DR. ROUTH: So two great questions, and I'll take the first one, that of the mandating vaccination for critical infrastructure workers such as healthcare providers or emergency personnel. I think we have not discussed that. It's hard to mandate a vaccine. I know even in my own experience hospital systems have a hard time even mandating seasonal influenza vaccine for healthcare providers. And I think this would be something similar.

I think what we need to do rather than mandating vaccine is really to build trust and confidence in these vaccine candidates. And I think that's what we're really trying to do through our

Vaccinate with Confidence strategy. I'd much prefer rather than mandating the vaccine to build that confidence in our healthcare provider infrastructure because it sort of gets at two issues.

One is that you're protecting healthcare providers as they're doing their daily work, but the second point is that it really does allow them to feel confident in the vaccine and recommend it to their patients. And so then we continue to spread that message out to the general public. So I would say, to answer that, I would really prefer to move forward with the work that we're doing around Vaccinate with Confidence rather than thinking through a mandate for COVID.

The second question around PPE, I think at this time we don't have information yet on the effectiveness data of these vaccines once they are rolled out into the general public. And so at this time, I would say we would want to continue to encourage good PPE practices, handwashing, masking, et

cetera, until we have some better understanding of what the effectiveness is of these vaccines as they're being rolled out. Thank you.

DR. MONTO: Dr. Lee, please be brief. We're eating into our lunch.

DR. LEE: Thank you for the presentation. One question I have is, as you know, some of the doses -- or some of the vaccines have two doses, and what are the plans to ensure people do come back for the second dose, which is either perhaps 21 or 28 days? Thank you.

DR. ROUTH: Right. So we are going to have some electronic and texting reminder systems in order to make sure that people do return for their second dose. I think the other critical piece, as I mentioned, is making sure that they do have a good experience with their first dose administration, making sure that they get their questions answered, making sure again they feel confident in their decision to get vaccinated. And I think that will go a long way to

ensuring that they do return. But we do have measures in place, again text message system and other electronic systems, to remind people. Everybody's busy, and I know it's easy to forget.

DR. LEE: Thank you.

DR. MONTO: Dr. Kurilla?

DR. KURILLA: Thank you. Beyond vaccine hesitancy, given that all of these -- so many vaccine manufacturers will be coming out with all sorts of press releases about the status of their vaccine and the Phase 3 data results will be coming along in drips and drabs throughout and given that companies tend to try to take advantage of every promotable advantage, the potential is set up that there will be vaccines available, either licensed or under EUA. But something better may be coming along in another two or three months, and people want to wait. Have you thought about how that messaging is going to go so that everyone is just not waiting for the perfect vaccine?

DR. ROUTH: We've definitely been thinking

that through, and, as you rightly point out, there are lots of different vaccine candidates right now. Some are two doses. The ones that may be coming later are a single dose. So I think it is -- that together with some of the work that we've done to understand vaccine hesitancy does make a case that people may be waiting to see what those first candidates are and whether they should wait for a more, quote/unquote, favorable candidate.

I think that's not the message we want to convey, so we're working hard within our own strategy to help people understand that vaccination is one of the key tools that we have to start to get our lives back on track and the things that we like to do -- visiting friends and family. Vaccine's a way to do that. So I do think we are going to really lean forward into the promotion of the vaccines that are available and make sure, again, that we have a wide footprint to get them out and available to people as quickly as possible.

DR. MONTO: Mr. Toubman?

MR. TOUBMAN: Yes, thank you. I have a concern about the allocation and prioritization with regard to people living in congregate settings. There's been a lot of discussion about nursing homes for obvious reasons. We have a very high percentage of deaths occurring there. But in jails, prisons, mental hospitals, and other congregate living situations where social distancing is just not possible, hygiene's very difficult, I'm wondering if CDC is looking at prioritizing all congregate living settings.

DR. ROUTH: Yes. So I will tell you I don't have information on that yet. I know that ACIP is still in deliberations around that prioritization structure. I think we did get some information from the National Academy of Science on their prioritization scheme. But ACIP will be doing their own deliberations and coming up that once vaccine candidates are moving forward into that authorization. So at this time, I think I can't answer your question completely, but I

know we are certainly taking people living and working in congregate settings under consideration in that prioritization scheme.

DR. MONTO: Okay. And finally, Dr. Cohn?

DR. COHN: Thank you. I just want to thank Dr. Routh for her great presentation and clarify one point, which is just for the public record that the federal government cannot mandate vaccines. So mandates have been shown to increase coverage in some settings, but the federal government would not be mandating use of these vaccines. Organizations, such as hospitals, with licensed products do have capability of asking their workers to get the vaccine. But in the setting of an EUA, patients and individuals will have the right to refuse the vaccine.

DR. MONTO: Okay. Well, thank you very much and thanks to all the presenters. As I promised, we are going to start again at 1:30. We will be, at that point, only 15 minutes late. So I think we're doing very well. Thank you all and see you at 1:30.

[LUNCH]

COVID-19 VACCINE CONFIDENCE

DR. MONTO: -- from Susan Winckler and Chris Wilkes about COVID-19 vaccine confidence. They're from the Reagan-Udall Foundation.

MS. WINCKLER: Thank you, Dr. Monto, and good afternoon. We're really pleased to be able to join you today. The Reagan-Udall Foundation is a nonprofit, nongovernment organization that was created by Congress solely to advance the mission of the FDA, so recognizing that we're likely less well known than the other organizations that have been presenting today. I'm joined by my colleague, Dr. Chris Wilkes, who was the lead researcher for the project that we will discuss.

So as part of our purpose to advance the mission of the FDA, today we will present one of our

pandemic projects. And specifically that's the COVID-19 Vaccine Confidence Project. As mentioned by prior speakers, uptake of the COVID-19 vaccine will be really important when we get to the point where there is an authorized or an approved vaccine or vaccines available. In this project, we are working with CBER to help them to understand the public perceptions about COVID-19 vaccines and the Center's role in vaccine approval or authorization and to identify what information key audiences want as they determine whether to receive an approved or an authorized vaccine.

I'll walk through the stages of our project, but we're focusing on two specific populations in frontline workers, as well as often underrepresented communities. And the goal is to work quickly to develop some information that will be helpful to the Agency. I want to note that this is a rather narrow project, looking at FDA's role and then key audience's interest or questions that they may have about that

role in a COVID-19 vaccine and how it is that CBER might respond to those questions or concerns.

Our project goes through a four-step approach. And so we began in August and September doing a quick analysis of key themes in the media and social media. And this was to help inform our listening sessions. So this was to see what is it that's being reported in the media as a dynamic or questions or concerns about a COVID-19 vaccine.

We are then conducting listening sessions. And we are deep in this stage right now. And our intent here is to listen to opinions and attitudes from different groups about a COVID-19 vaccine. We're distinctly in this stage gathering information. So we are listening in these sessions. We are not responding nor educating but rather listening to what it is that the participants in these discussions say. We'll then take that information -- take what we heard and construct approaches for how one might respond. And there we'll be looking to develop messages or responses

that respond to those concerns or questions, as well as teeing up the messengers who would be best positioned to deliver those messages and then to test the messages and messengers to assure that they're relevant and credible to key audiences.

So our focus today is to report out our initial insights from these listening sessions. As I noted before, we have two key audiences. And in particular, we're looking and hearing from frontline workers and then traditionally underrepresented groups.

In the frontline workers, we're conducting sessions in those who work in retail, within healthcare systems, and then some in community health. In the traditionally underrepresented groups, we've talked about this within our project. This is prioritizing those whose voices are often not heard and trying to make sure that we hear from them about their concerns and opinions. And so here, we're conducting listening sessions with African American/Black men and women, the Black and Latinx community leaders, English as a second

language, and two different approaches in indigenous and Native people. So those are who we are hearing from.

The bulk of my presentation -- of our presentation, we'll share what we are hearing. We've conducted eight listening sessions to date and have four or five more in the queue to complete in the next few weeks. As a component of these listening sessions, we assure the participants that we will not connect them with specific comments but rather that we will protect their information. What we're going to do in the next few slides is to share with you direct quotes from these listening sessions.

So we have organized some of these quotes into themes that are emerging so that we can share them with you. As we've described these sessions, you could sum it up and say that they have been powerful, illuminating, and sobering. And I hope as we share these direct quotes as an illustration of what we're hearing that you too will have the opportunity to learn

from these sessions.

I'll note that in presenting these quotes we aspire to share the words of the listening sessions participants, but we do not intend to replace their individual voices with our own. But to assure that the words are heard, what I will do is introduce the theme for each slide, and then my colleague, Dr. Chris Wilkes, will read the direct quotes from the sessions. So I'll just note the next six slides, these are direct quotes from the listening sessions that we have conducted. The first theme that we heard is a concern about the speed of the process and how quickly it is that things are moving forward. Dr. Wilkes?

DR. WILKS: "The speed is appreciated, but there are questions. They want to get one out as soon as possible, which I don't think is very safe. We all know how long vaccines take, so to hear that it will be ready in a few months is concerning. I would not be first in line, and I would want to see some data. Vaccines takes years to develop and test. For them to

try to do it in a year is pretty absurd."

MS. WINCKLER: Thank you. The next concern was a specific distrust of government and government agencies.

DR. WILKS: "Who can we trust? That's the million-dollar question. I also hear so many people arguing about the pros and the cons, mostly cons because of distrust of the government from past experience. When COVID first came out, I trusted the CDC website and was sharing from there. Now I trust the FDA and CDC much less than I did when this first came out. I don't think the FDA can be trusted to keep people safe. When I hear the FDA say that they have a particular process but then I hear the White House say they can cut it in half or negate it, that brings more distrust."

MS. WINCKLER: Thank you. This distrust, however, was not limited to government but rather extended to components of the broader healthcare system. Dr. Wilks?

DR. WILKS: Thank you, Susan. "I'm looking for an organization I can trust that does not have a tainted history and has not been bought out by some big pharma. Our family has had issues and a wrongful death suit with local -- wrongful death with local hospitals. I have a major distrust. I have become really not trusting of the medical establishment. They never answered my questions. Doctors are going to be pushed to see this, the vaccine, to our community. I would not like you to sell me but show me and tell me, educate me. African Americans are treated differently by doctors."

MS. WINCKLER: Another emerging theme is concern that politics and economics will be prioritized over science. Dr. Wilks?

DR. WILKS: "I would love to take it, the COVID-19 vaccine, because my wife is asthmatic. So if I can prevent me being sick, I can prevent her from being sick. But I'm suspicious that they're trying to get it out before the election. A lot of people don't

trust the people who are making the vaccine because they're politically motivated, and we are all a bunch of guinea pigs. There's a common feeling that economic considerations are being considered over people's health. Time and time again the U.S. has proved it is about the dollar, especially in healthcare. For me to make my decision to trust myself with the information, I would have to hear from countries who take better care of their people."

MS. WINCKLER: Another insight relates to fear that the vaccine will not work for individuals or for their community. Dr. Wilks?

DR. WILKS: "I need to know that minorities who took it are okay. I need to know it works for everybody. I'm not trying to be harmed. Indian people are different biologically, but then who constitutes as Indian, half Indian? Unless there's a specific study done with us and our specific makeup, we're going to be incidentally immune with a vaccine that is studied with a proportionately lower number of participants in the

study group. I need to know other minorities have taken it. Are other minorities okay? We're all built different. How do we know?"

MS. WINCKLER: The final emerging insight grounds us in a reality that a COVID-19 vaccine will be used in a system in a nation with racial and ethnic disparities and discrimination.

DR. WILKS: "I firmly believe that this is another Tuskegee experiment. I stand strong on this in saying that my family's personal belief is that the vaccine would be an experimentation on us, and that's not something I'm willing to risk, not something I'm willing to do. One of my biggest concerns is that Alaska Natives, Indigenous people are at the highest risk of death, and we are the ones that are the guinea pigs for the rich. They want to use us, and I don't want to keep getting used. We're not going to be guinea pigs again. The more they study me, the more they know how to get rid of me."

MS. WINCKLER: This concludes the direct

quotes from our listening sessions, but I hope that you found them illuminating. As we aspired here, our intent was to gather the concerns to then help be able to generate the responses to those concerns and questions. So in a manner that's consistent with CDC's slides before the break, we know we have a lot of work to do in this space.

And here are some of our initial learnings: that there is interest in the science and how the science relates to individuals; that they want to understand the process and for it to work; when we think about messengers, that personal relationships will matter with doctors and other healthcare providers; and that timing matters in perceptions of safety on at least two levels, both in development and in uptake of a vaccine. Some of our listening sessions participants noted that they would want to wait months or even years before choosing to receive a vaccine. There's also a fifth dynamic in that when we conducted these sessions the individual focused on a COVID-19

vaccine.

MR. KAWCZYNSKI: Dr. Winckler? Dr. Winckler, I think -- somebody can confirm, but does anybody else hear Dr. Winckler?

DR. MONTO: I can't hear her at all, Mike.

MR. KAWCZYNSKI: Chris Wilks? Yeah. She dropped audio. I can see that. Dr. Wilks?

UNIDENTIFIED FEMALE: I can't hear her or Dr. Wilks. Are you able to hear her now?

MR. KAWCZYNSKI: Yeah. They're reconnecting. Here she comes. Here comes Dr. Winckler. We'll just give her a second. Just bear with us. I see Dr. Winckler coming right back in. Just one minute. Yep. I think her phone disconnected. It happens. There you go. Welcome back, Dr. Winckler.

MS. WINCKLER: So our next steps, as I had mentioned (audio skip) listening session. (Audio skip).

UNIDENTIFIED MALE: She's coming through garbled.

MR. KAWCZYNSKI: Yes, Dr. Winckler, you've got to bring the phone closer to your mouth. I think you got -- give us a sound check quick. I think your earbud disconnected.

MS. WINCKLER: Is that better?

MR. KAWCZYNSKI: Go ahead.

MS. WINCKLER: And so finally we'll (audio skip).

DR. WILKS: Are there any questions for us?

DR. MONTO: Why don't we go on to the next presentation because the time's expired anyway. Okay. I'd like to introduce now Dr. Jerry Weir, Director of the Division of Viral Products at OVRR. He will be talking to us about licensure and emergency use authorization of vaccines to prevent COVID-19: chemistry, manufacturing, and control considerations. Jerry.

LICENSURE AND EMERGENCY USE AUTH OF VACC TO PREVENT COVID-19: CHEMISTRY, MANUFACTURING & CONTROL CONSIDERATIONS

DR. WEIR: Thank you and good afternoon. This will be a fairly short presentation. What I'm going to try to do is describe briefly the role of the CMC -- Chemistry, Manufacturing, and Controls -- in licensure and EUA use and by using a few key examples try to illustrate the complexity and the importance of CMC in both of these processes. The next two slides are going to give just a brief background.

Chemistry, manufacturing, and controls and facility information and data are critical to ensure the quality of vaccines and the consistency of vaccine manufacture. Licensed vaccines must meet statutory and regulatory requirements for quality manufacture and control. You heard this in the introduction earlier this morning. All vaccines must be safe, pure, and potent. And manufacturing and facilities must be in

compliance with applicable standards. But also, sufficient information must be provided for vaccines that will be used under Emergency Use Authorization to ensure vaccine quality and manufacturing consistency.

As you've also heard many times today, COVID-19 vaccine development may be accelerated based on knowledge -- it may be accelerated. And some of that acceleration may be based on knowledge gained from similar products manufactured with the same well-characterized platform technology. What this means is that some aspects of manufacture and control may be based on the vaccine platform. But I want to stress at the very start here that any CMC data that will not be available at the time of licensure or at the time of an EUA issuance must be discussed with the FDA in advance, sufficiently justified, and judged to have minimal impact on product quality.

In the next two slides, I'm going to give a few key expectations for licensure of COVID-19 vaccines. This is just a brief high-level overview of

some of these expectations. Much more detail is provided in the guidance that was put out in June, so you can look there for more details on all of these aspects.

But what we would expect for a COVID-19 vaccine is complete details of the manufacturing process. This includes history of process development capturing all changes incorporated into the manufacturing process, information documenting adequate control of all source material, and establishment of a quality control system for all stages of manufacturing. We would also expect validation of the manufacturing process. This includes data to support consistency of the manufacturing process across all manufacturing sites.

We would expect establishment of a quality control unit. This particular demonstration that quality release tests, including key tests for vaccine purity, identity, and potency are suitable for their intended purpose and validated. A few more

expectations, we would expect the establishment of comprehensive stability program, including the demonstration of final container stability and expiry date and demonstration that the vaccine potency is maintained throughout expiry. We would expect compliance with all applicable standards for manufacturing sites, including validation of major utilities and qualification of all equipment, validation of aseptic cleaning and sterilization processes, establishment of a quality control unit that has responsibility for the oversight of manufacturing. And the last one that I have listed is establishment of a lot release protocol for product distribution.

Next, I'm going to turn to emergency use authorization. This slide just gives a high-level overview of some of our considerations. To enable FDA to conduct a meaningful review, an Emergency Use Authorization request for a COVID-19 vaccine must include CMC data, identification of the manufacturing sites, and information with respect to current GMP. It

is critical that adequate manufacturing information be provided to ensure the quality and consistency of EUA vaccines. The manufacturing and process control data will need to be submitted in advance of an EUA request. The CMC information and data that we would expect -- and it would be needed to support the use of a COVID-19 vaccine under EUA -- are generally similar to that needed for licensure.

In the next two slides, I'm going to once again just highlight some of the key expectations. Again, these are provided in much more detail in the recently released guidance document earlier this month. So this is sort of a high-level overview. You'll notice italics in some of the bullets that follow in this slide and the next slide, and all that means is that I put them in italics just to sort of point out some slight differences with the licensure process.

But here are some of the key expectations from our guidance document. For EUA application, we would expect, again, complete details of the manufacturing

process. We would expect validation of the manufacturing process. We would expect establishment of a quality control unit. We would also expect a stability plan that includes tests for product safety, quality, and potency and stability data from all available developmental and clinical lots to support the use under EUA. This stability data would be necessary to support investigational use of the product under EUA. We would also -- okay.

I want to say that expectations for manufacturing facilities will be similar to those for licensure. This was brought up earlier this morning in one of the questions, and it's true that the inspection process -- this technically applies to the licensure process. But as I've already pointed out a couple of slides ago, we have made it clear that we expect at the time of (audio skip) submission for an EUA application that all manufacturing sites be identified as meeting compliant status. And what we are expecting to do is that we will have GMP compliance assessed using site

visits and other submitted information to ensure that the products and the manufacturing facilities are GMP compliant.

And finally, the last one that I've listed is that the appropriate quality specifications established for all drug product lots used under EUA and testing results would be submitted at the time of vaccine distribution. The reason I mention this one is because the FDA regulation for lot release does not apply to investigational products, including those distributed in (audio skip). Oh, I'm back. Okay. The reason for this -- to pointing this out is because even though the lot release -- or FDA regulation for lot release does not apply to investigational drugs, we expect to obtain essentially the same information in other ways.

And I'll summarize in the last slide this entire presentation about CMC considerations for licensure in an Emergency Use Authorization. A manufacturing process that ensures product quality and consistency is necessary, whether a vaccine is

considered for licensure or for use under EUA. The CMC expectations will be the same for all COVID-19 vaccines, but the manufacturing and control data are going to be unique for each product and each production process. And finally and importantly, the confidence and reproducibility of safety and efficacy results from pivotal clinical trials depends on the establishment and maintenance of high standards of vaccine quality control and manufacturing.

I'll stop there. Hopefully, we made up a few minutes. I can either take questions now, or I guess we could wait until after the next presentation on clinical considerations. That's up to you, Dr. Monto.

DR. MONTO: Right. And thank you, Dr. Weir, for making up the time. I think it would be most efficient if we wait for questions until after Dr. Fink's talk. So we'll go ahead and hear from Dr. Doran Fink about the clinical considerations of licensure and emergency use. Dr. Fink?

LICENSURE AND EMERGENCY USE AUTH OF VACC TO PREVENT COVID-19: CLINICAL CONSIDERATIONS

DR. FINK: Thank you, Dr. Monto. So I want to start off by repeating something that you've heard several times today. And that is in the context of the worldwide effort currently underway to develop safe and effective vaccines to address the COVID-19 pandemic as quickly as possible, CBER is committed to ensuring that COVID-19 vaccines are safe and effective by relying on sound science, established regulatory standards, and transparent decision making in our review of COVID-19 vaccine candidates. We need to make sure that we're doing these things to ensure that any COVID-19 vaccine approved or authorized for widespread use will be safe and will have a meaningful impact on the pandemic. But just as importantly, we need to ensure public trust and confidence in COVID-19 vaccines and vaccines in general. And you heard some of the concerns expressed by the public in the presentation by the people from

Reagan-Udall.

So to ensure transparency about our processes and our decision making, we've released two guidance documents that you've heard about several times today and that are included in the briefing package. Now, on this presentation what I'm going to do is to summarize and explain what we consider to be the most important clinical considerations from these guidance documents to inform the Committee's discussion. First, I'll cover clinical data to support licensure of COVID-19 vaccines as laid out in our June guidance. Then, I will talk about clinical data to support Emergency Use Authorization of COVID-19 vaccines as detailed in the guidance document released earlier this month. And then I will end the presentation with a discussion of continued evaluation of COVID-19 vaccines following either licensure or EUA, borrowing from both guidance documents.

To lay the ground rules, I want to remind the Committee and the public that CBER has an expectation

for randomized, blinded placebo-controlled trials to provide direct evidence that a vaccine protects against SARS-CoV-2 infection and/or disease. We consider that such trials should be feasible given the current COVID-19 disease epidemiology, and also understanding of how vaccine-elicited immune responses might predict protection is currently too limited to infer vaccine effectiveness from immune responses alone in the absence of clinical data providing direct evidence of protection. In our guidance document, we've stated that clinical trial to support licensure should enroll adequate numbers of subjects representing populations most affected by COVID-19. These include racial and ethnic minorities, elderly individuals, and individuals with comorbidities associated with increased risk of severe COVID-19. We've also stated that it's important to examine safety and effectiveness data in previously infected individuals because, in practice, pre-vaccination screening for prior infection is unlikely to occur.

There are a variety of effectiveness endpoints that could be evaluated in phase three trials for COVID-19 vaccines. Most of the trials underway currently are evaluating COVID-19 disease of any severity. However, most of these trials also include endpoints related to more severe COVID-19 disease and also SARS-CoV-2 infection, whether or not symptomatic. We have recommended standardized case definitions to be used in pre-specified analyses for both disease of any severity and also severe disease. However, we have not specified any requirement or preference for a specific endpoint to be used in the primary analysis of vaccine effectiveness. Again, most of the studies currently under way are using disease of any severity as the primary endpoint to be analyzed.

Now, we have released what we consider to be minimal criteria to support the effectiveness of COVID-19 vaccines. But before I get into what those criteria are, I want to spend this slide explaining why we've set this standard. The reasons we consider such a

standard to be important is because widespread deployment of a weakly effective COVID-19 vaccine could result in more harm than good.

It could do so by providing a false sense of security that interferes with measures to reduce SARS-CoV transmission, such as wearing of masks and other PPE and social distancing. It could interfere with development and evaluation of potentially better vaccines that could have a greater impact on the pandemic. And it could potentially allow for even less effective vaccines to be deployed based on meeting noninferiority criteria for relative effectiveness, a phenomenon known as bio-creep. Without sufficiently stringent criteria, a COVID-19 vaccine candidate could be declared effective just by chance. And the risk of declaring a weakly effective vaccine and deploying a weakly effective vaccine increases as the number of vaccines being evaluated in Phase 3 trials increases.

So here's the standard that we've outlined. What we've said is that the success criteria for

primary vaccine efficacy endpoint analysis to support licensure of a COVID-19 vaccine includes that the point estimate for vaccine efficacy versus a placebo comparator should be at least 50 percent. And the appropriately alpha-adjusted confidence interval lower bound should be at least 30 percent. These are what we consider to be minimum criteria.

Clearly, it would be great if a vaccine could be demonstrated to be much more effective, and we certainly wouldn't argue with development programs that are designed to show that vaccines are more effective than these minimum criteria. We've also outlined that secondary efficacy endpoint analyses to further inform protective effect and to be described in vaccine labeling could be tested against a less stringent lower bound, greater than zero percent. However, this testing would be contingent upon meeting the primary endpoint criteria first.

We also recognize that there are some populations for which it may not be feasible to

directly demonstrate vaccine effectiveness using a clinical disease endpoint, for example, pediatric populations where the attack rate of symptomatic COVID-19 disease is much lower than in adults. And so for these populations, following direct demonstration of protection in another population -- for example, adults, as are currently being evaluated in ongoing Phase 3 trials -- effectiveness of the same vaccine could be inferred in a second population by immunobridging. This immunobridging approach would be based on comparison of one or more immune response biomarkers between populations using pre-specified criteria and presumed that disease pathogenesis and mechanism of protection in each population are similar.

Turning now to data to support safety of a licensed COVID-19 vaccine, I want to reiterate that our general expectations are no different than those for safety data that have supported licensure of other preventative vaccines. And this includes a safety database of at least 3,000 subjects in relevant age

groups exposed to the vaccine regime intended for licensure, so just to be clear, a safety database of at least 3,000 younger adults and at least 3,000 elderly subjects. We don't anticipate any issues with meeting this standard for COVID-19 vaccines that are currently in Phase 3 trials. These trials are enrolling substantially larger databases and will have a placebo control group as well.

Our guidance document goes into additional details about safety data needed to support licensure. For sake of time, I'm not going to go into those details right now. There are some additional considerations that are important to the benefit-risk assessment for COVID-19 vaccine because these considerations may have limited data to address them at the time of a successful case driven interim or final efficacy analysis.

We may know very little at the time of a successful efficacy analysis about the durability of protective immunity elicited by the vaccine, the

effectiveness of the vaccine against the most severe and clinically significant manifestations of COVID-19, the potential risk of enhanced respiratory disease associated with waning of vaccine-elicited immunity, as well as limited longer term safety follow up. And therefore, even following a successful efficacy analysis that meets our pre-specified criteria, additional follow up would still be warranted to further inform the benefit-risk assessment for licensure, as well to inform labeling. And I'll talk about that a little bit more in the last third of my presentation.

I'm going to turn now from licensure to Emergency Use Authorization. As you've heard earlier today, an Emergency Use Authorization for a COVID-19 vaccine may be requested to allow for the vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. And in this scenario, a determination that a COVID-19 vaccine's benefits outweigh its risks would require

data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and effectiveness sufficient to support such widespread use. I want to make sure that everyone understands that, as with vaccine licensure, issuance of an emergency use authorization would specific use only in those populations for which the available data support favorable benefit/risk.

Just as with licensure, an EUA request for COVID-19 vaccine may be supported by a case driven interim analysis from one or more clinical trials. However, this type of case driven interim analysis may come very quickly with the large clinical trials currently underway, especially if attack rates are very high. So to support a favorable benefit/risk determination, again taking into account that we're contemplating the potential rapid and widespread deployment to millions of individuals, including healthy people, we consider that vaccine effectiveness to support issuance of an EUA should first of all

demonstrate direct evidence of protection against SARS-CoV-2 infection or disease and secondly should demonstrate a vaccine efficacy point estimate of at least 50 percent versus placebo with an appropriately alpha-adjusted confidence interval lower bound greater than 30 percent. You'll see that these are the exact same criteria that we consider necessary to support vaccine licensure.

But meeting these efficacy criteria is not the only information that goes into a benefit/risk assessment. Additionally, analyses intended to support issuance of an EUA should ensure that vaccine effectiveness is assessed during the time period when adaptive and memory immune responses, rather than innate responses, are mediating protection. These are the type of responses that would be most relevant to the vaccine having an impact on the pandemic. The analyses should also allow for early assessment of waning protection and potentially associated risk of enhanced respiratory disease. And finally, they should

ensure adequate safety follow up to inform a benefit/risk determination.

So taking these considerations into account, what we've outlined in our guidance document is that we consider an median of two months to be the minimum follow up duration that could support a favorable benefit/risk determination to issue an Emergency Use Authorization for a COVID-19 vaccine. And just be clear, what this means is at least 50 percent of participants will have two months of follow up for both safety and effectiveness following completion of the full vaccination regimen. To explain a little bit further the safety considerations that informed our selection of a two-month median follow up duration, historically, uncommon but clinically significant adverse events plausibly linked to vaccines -- for example, immune mediated adverse reactions -- generally have onset within six weeks following vaccination. And therefore, the median follow up duration of two months allows time for potential immune-mediated adverse

reactions to be observed and evaluated.

Taking these safety considerations into account, as well as considerations around timing of protective immunity that I discussed in the previous slide, we've advised vaccine manufacturers conducting Phase 3 clinical trials that they're timing of interim analyses for vaccine efficacy should account for these expectations for follow up to support an EUA. Our EUA guidance has also described some additional expectations for safety data to support a benefit-risk assessment. First, we expect that Phase 3 safety data will include a high proportion of enrolled subjects numbering well over 3,000 vaccine recipients who have been followed for serious adverse events, adverse events of special interest, for at least one month after completion of the full vaccination regime.

For the large Phase 3 trials that are currently underway that enrolled subjects at a very rapid pace at the beginning of the trial, we do not expect this expectation to cause any problems. It's in

the guidance more to cover a scenario for a relatively much smaller and/or much more slowly enrolling clinical trial that might reach a successful efficacy analysis, for example, due to high attack rates. Secondly, we expect that solicited adverse reactions will be characterized in an adequate number of subjects in each protocol defined age cohorts. Thirdly, we expect sufficient cases of severe COVID-19 in placebo recipients, cases that have been collected in the same timeframe as primary endpoint cases, so that we can assess the case splits between vaccine and placebo groups looking for signals of both vaccine effectiveness against severe disease and also for enhanced respiratory disease.

In our guidance document, we mentioned five cases in the placebo group as being generally sufficient to meet this expectation. However, in cases where the vaccine efficacy point estimate and lower bound are both exceptionally high and there are no severe cases in the vaccine group, fewer than five

cases may be acceptable. Finally, we have requested that all safety data accumulated from Phase 1 and 2 studies conducted with the vaccine, focusing on serious adverse events, adverse events of special interest in cases of severe COVID-19, also be included in an EUA submission. This is important because these data from studies that were initiated earlier will include longer duration of follow up.

For the last part of my talk, I'm going to discuss considerations for continued evaluation of COVID-19 vaccines following licensure or EUA. We've heard a number of more detailed talks from CDC and also FDA on the potential mechanisms for conducting this type of continued evaluation. In terms of safety, it is inherently obvious that safety monitoring during rapid and widespread deployment of a COVID-19 vaccine will be needed to detect and evaluate adverse reactions that may be too uncommon to detect even in large clinical trials, apparent only after additional time to come to medical attention, or relevant to specific

populations with limited safety data at the time of vaccine deployment -- populations such as pregnant women, persons with prior SARS-CoV-2 infection or individuals with immunodeficiency conditions.

In terms of effectiveness, longer term data on COVID-19 outcomes following licensure or EUA would further characterize duration of protection; determine vaccine effectiveness in populations not included in the initially authorized or approved use; further evaluate effectiveness against specific aspects of SARS-CoV-2 infection or disease, such as disease transmission; investigate immune biomarkers that might predict protection; and finally, further assess the theoretical risks of enhanced respiratory disease and other potentially immune-mediated complications following vaccination and subsequent exposure to SARS-CoV-2.

We consider that evaluation of a COVID-19 vaccine after licensure or EUA should occur through a combination of pharmacovigilance activities, including

both active and passive safety monitoring during deployed use of the vaccine; continuation of blinded follow up in ongoing placebo-controlled trials for as long as is feasible; and observational studies, including those that leverage healthcare claims data, to evaluate safety and effectiveness outcomes. You heard about these types of observational studies in presentations given earlier in the day. Additionally, CBER may require post licensure studies to address known or potential serious risk identified during review of a licensure application.

We touched very briefly on passive safety monitoring, which you heard about from CDC. This will occur using established reporting mechanisms such as VAERS and direct reports to the vaccine manufacturer. What I'd like to highlight on this slide is that our EUA guidance directs that any EUA request for a COVID-19 vaccine should include a plan for active safety follow up of persons vaccinated under the EUA. This active safety follow up should monitor for deaths,

hospitalizations, and other serious or clinically significant adverse events and will be critical to inform ongoing benefit-risk assessments for continuation of the Emergency Use Authorization.

I want to spend the last two slides talking about continuation of placebo-controlled trials. In our EUA guidance released earlier this month, we stated that CBER does not consider issuance of an EUA for a COVID-19 vaccine in and of itself as grounds to immediately unblind ongoing clinical trials and offer vaccine to placebo recipients. The reason why we have made this statement is that a COVID-19 vaccine made available under an EUA will still remain investigational. As I've outlined in previous slides, safety and effectiveness data to support an EUA may be collected under a relatively short follow up period, a median of two months following completion of the vaccination regime, much shorter if compared with data that have supported licensure of other preventative vaccines and shorter than the follow up that we would

expect to support eventual licensure of a COVID-19 vaccine. Therefore, continuation of placebo-controlled follow up after Emergency Use Authorization will be important and may actually be critical to ensure that additional safety and effectiveness data are accrued to support submission of a licensure application as soon as possible following an Emergency Use Authorization.

Given these considerations, a discussion of the conditions and the timing that would make unblinding of an ongoing clinical trial imperative deserves careful thought and attention, as does consideration of the possible mechanisms that could be used to replace loss of such follow up. Once a decision is made to unblind an ongoing placebo-controlled trial, that decision cannot be walked back. And that controlled follow up is lost forever. We do recognize that following issuance of an EUA there will be interest among study participants to receive vaccine under the EUA. And therefore, any EUA requests for COVID-19 vaccine should include strategies to ensure

follow up in ongoing clinical trials and to handle loss of follow up due to withdrawal of participants, including those who withdraw in order to seek vaccination under the EUA.

I would also like to note that availability of a licensed vaccine does not automatically preclude continuation of blinded placebo-controlled trials, specifically in populations for which the licensed vaccine is not yet approved for use and in populations for which the licensed vaccine is not sufficiently available to address public health needs. However, we do acknowledge that situations will likely arise where it is no longer ethically permissible and therefore no longer feasible to continue placebo-controlled follow up in an ongoing trial or to initiate a placebo-controlled trial. In those situations, if widespread availability of a licensed COVID-19 vaccine precludes use of a placebo comparator, then the licensed vaccine could be used as a comparator to evaluate relative vaccine efficacy of other vaccines, testing the

confidence interval lower bound against a non-inferiority margin.

These types of non-inferiority trial designs require much larger sample sizes than placebo-controlled trials. And so feasibility will certainly be an issue, but there may be innovative and novel clinical trial designs that could help to reduce the size of such trials. We are also aware that there's interest in inferring effectiveness of a vaccine solely from comparison of immune responses between vaccines, i.e. comparing a new vaccine to one that has directly been demonstrated to be effective. However, such an approach would require further discussion, as currently the understanding of mechanism of protection is too limited to support this approach. That's the end of my talk, and I will open it up to any questions.

DR. MONTO: Thank you, Dr. Fink. Very intriguing presentation raising many questions. And what I would like to start our question period with is a question about what the advantage of seeking an

Emergency Use Authorization would be given the fact that the primary outcomes is the same? And a corollary, if somebody does get emergency use authorization, how then do they get full licensure?

DR. FINK: Thank you for that question. So I did outline in my presentation several differences in the data that would be expected to support Emergency Use Authorization versus the data that would be expected to support licensure, mainly related to duration of follow up. In terms of safety data, we typically require a reasonably sized safety database with at least six months of follow up to support licensure. We would not have any different expectation for COVID-19 vaccines.

For an Emergency Use Authorization that is intended to address an ongoing public health emergency, what we've outlined is that a conclusion of favorable benefit/risk could be made based on meeting the same standard for vaccine effectiveness that would support licensure but with an abbreviated follow up for both

safety and effectiveness. The abbreviated follow up for effectiveness, I think, is equally important. At the time of an interim analysis, we may see a point estimate that is very high.

In fact, the point estimate would have to be high in order for a smaller number of cases to meet our requested success criterion for the lower bound around that point estimate. However, because of the relatively smaller number of cases, the confidence interval would be very broad. And so additional follow up to further design and get more certainty in vaccine effectiveness would be another important consideration separating the data used to support Emergency Use Authorization versus those data that would eventually be submitted to support vaccine licensure.

DR. MONTO: And if there is Emergency Use Authorization, then the longer follow up, et cetera, would be required to get licensure as long as the studies continue -- or some studies continued to be blinded, correct?

DR. FINK: We have advocated for a continuation of blinded follow up in the ongoing trials. That's correct.

DR. MONTO: And that could result in full licensure -- getting a BLA?

DR. FINK: That is correct.

DR. MONTO: Okay. Dr. Kurilla?

DR. KURILLA: Thank you, Arnold. I actually have one question for Jerry and one question for Doran. The question for Jerry is, with regard to CMC requirements, can you briefly outline what a BLA would contain that you would not expect for the EUA? What extra would you be getting? That's my question for you. And then for Doran, did you consider at all the possibility of an expanded access protocol for those specific groups that you would issue the indication for the EUA instead of an EUA?

DR. WEIR: You want me to go first since yours to me was the first question? As I pointed out somewhere in the talk, the CMC expectations are very

similar for EUA use or licensure. There are some differences though. I'll give you one quick example.

You may have noticed that I mentioned something about stability. For example, when a manufacturer comes in and licenses a product, by that time they have enough data to support a shelf life or an expiry date of whatever period of time. Under Emergency Use, we don't expect to have that much information. We only want to know that -- because, as Doran pointed out, it's still under investigational use, we want to have enough stability data to ensure that it's being used as under EUA that it is stable for that period. That would be one not subtle difference between what we would expect in licensure versus a product under EUA.

So there are a few things like that. I mentioned the inspection program is some slight differences. The lot release protocols and process is a little bit different. So there's some differences like that. But generally, the expectations are very

similar.

DR. FINK: Yeah. So to answer your question about an expanded access protocol, that is another regulatory mechanism for providing access to investigational vaccine. I think if we were to consider an expanded access protocol of the same size and scope as what is being considered for an Emergency Use Authorization, then the benefit/risk considerations and the data to inform those benefit/risk considerations and allow that type of use would be highly similar. The differences between expanded access use and Emergency Use Authorization are that expanded access use is done -- or is carried out under FDA's investigational new drug regulations.

So among many other things, those regulations require use of an institutional review board and also obtaining informed consent from recipients of the investigational vaccine according to regulations for clinical investigations -- research use of investigational vaccines. And so operationally

speaking, an expanded access protocol would add some complexity, and that is why Emergency Use Authorization is being considered primarily as the mechanism for addressing the public health emergency that has been declared.

DR. MONTO: Great. Dr. Notarangelo.

DR. NOTARANGELO: Thank you. My questions are actually for Dr. Fink. Thank you very much, Dr. Fink, for a very clear presentation. I really appreciate it. So you clearly mentioned the issuance of an EUA would not represent grounds for unblinding ongoing clinical trials. At the same time, one could imagine that those individuals, those subjects who volunteered in these trials obviously have an interest in vaccine development. So they might easily withdraw. A proportion of them might withdraw. Is this a matter of concern, and what strategies are you anticipating in order to keep a sufficient number of individuals enrolled in placebo-controlled trials?

And the second question is about the bridging

-- immunobridging that you mentioned when you refer to inferring data from the adult population to the pediatric population, which is an important issue because, as you mentioned, we are not enrolling in any of the trials a sufficient number of minors. Now, the problem with minors is that, as you well know, MIS-C is another different manifestation of the disease, which you don't see or you see in a much smaller proportion in adults. So inferring data from adult to kids might not be necessarily a good thing to do unless we have proven efficacy and staff of the vaccine also inoculating an MIS-C condition. I'd like you to comment on this as well. Thank you.

DR. FINK: All right. So first of all, with regards to mitigating the risk of dropout from ongoing clinical trials, we do share that concern. I don't have any specific remedies to offer at this time. We have asked the vaccine manufacturers and the other government agencies who are involved in conducting these trials to think carefully about how they would

ensure clinical trial retention. So we would like to hear from them in the EUA submissions that we might get.

In terms of pediatric development, we do recognize that there is still a lot to be understood about the pathogenesis of MIS-C and what differences there may be in COVID-19 disease manifestations comparing pediatrics versus adult populations. For the time being, we have considered that adolescents are sufficiently similar physiologically to adults. And in general, we have an established paradigm -- an established framework of age de-escalation once there is enough data, including both clinical and nonclinical data from animal studies to support the prospect of benefit in pediatric populations as well as sufficient safety data in adults to reasonably understand the potential risks in pediatric populations. So we have been advising vaccine manufacturers in their development programs to at least start with consideration of enrolling adolescents in clinical

trials, and then further considerations for lowering the age groups involved in vaccine development can proceed.

DR. MONTO: Dr. Offit?

DR. OFFIT: Yes, thank you. I think -- first of all, thank you both, Doran, and Jerry, for excellent presentations. I have a much better understanding now of what I think are largely the subtle differences between the EUA and sort of BLA licensure application for this vaccine. And I think it sort of outlines to me as what I think is our problem. I think we have a language problem. I think when people hear the term "Emergency Use Authorization," what they hear is not necessarily an approved or authorized product. They hear a permitted product, which is to say that you are permitted to use it as you would any investigational new drug or Phase 1 product, which is a very low bar.

So hydroxychloroquine was permitted for use; convalescent plasma was permitted for use, even though neither worked. That's not what we've been talking

about for the last two hours. What we've been talking about for the last few hours are large prospective placebo controlled trial, so 30,000 to 60,000, where we plan to include all groups for whom we would eventually use this product, including the elderly, those with different racial or ethnic backgrounds, people with various medical conditions, because we want to make sure that we have data in each of those groups that allows us to say we can then recommend these vaccines for that group.

So the sort of CMC subtle differences that Jerry was talking about or the more subtle, sort of clinical differences that you were talking about are not huge. This is much, much, much closer to what is typically a BLA licensure process than it is to how at least the public, or frankly I, perceive an EUA process. So I think we need to make that clear I think not just to the general public but to the medical public as we move forward what I think is a relatively high standard that we're holding these vaccines to.

These vaccines are about to be given to a lot of healthy young people who are unlikely to die from this virus, which is why you got the kinds of comments that you saw through Susan and Chris earlier. People think that there are critical safety guidelines or efficacy guidelines that are being curtailed, but that's really not the story. And I just wish we could get rid of the word EUA. I was going to make the recommendation let's just do it through a BLA and licensure process, but I see there are subtle differences that would make it so we couldn't do that, at least not initially. Am I right in this perception?

DR. FINK: Yeah. Thank you. I think you described the considerations very well. And yes, some of these differences are subtle, but some of them are not so subtle in terms of timing. And so what an EUA could accomplish would be to make a vaccine that has been vetted by very stringent criteria available much sooner than would be possible with a BLA -- with a licensure. So that I think is a key message is that

the evaluation criteria remain very stringent, but it does allow access sooner to address the pandemic.

DR. OFFIT: But yeah. I think that --

DR. MONTO: Dr. Offit, I think this is something we're going to have a lot of time to talk about during our discussion. I agree with you totally. That's why I asked my question about how different it is. And my concern also is that with issues of continued blinding that something that is given an EUA will never be able to get a BLA because of various issues. Any further -- before I recognize the next questioner, any further comments, Jerry?

DR. WEIR: I was just going to say that Paul got the point about why we considered what we were asking for very important. That was all.

DR. MONTO: Okay. Next is Dr. Meissner.

DR. MEISSNER: Thank you and thank you, Dr. Weir and Dr. Fink. I am much more reassured after hearing your presentation. So thank you for that. I have two questions that I would like to ask.

The first question is why did you select a 50 percent efficacy point for the vaccine? We know, for example, that last year's influenza vaccine's overall effectiveness among all age groups and all strains was 39 percent. And in view of the very large burden of disease, the argument is made that if there are 30- or 40,000 influenza infections in the United States each year, then a 39 percent reduction in the burden of disease is quite large and desirable.

Then, if I may, I'd like to ask you a second question that's a little bit more complicated. I agree strongly with the need for vaccine for children. I'm a pediatrician. We definitely need a vaccine for children. But I agree with the position that I think the FDA's taken is that COVID-19 in most children is not a severe disease. And I looked up the hospitalization rates this morning from COVID-19, and for children five to 17 years of age it's 0.9. And last year for influenza, the hospitalization rate was 42.1 per 100,000.

So COVID-19 in children is much less a severe disease than influenza. And in terms of hospitalization, mortality rates are higher for influenza than for COVID-19 in children. And I'm frankly a little concerned that Pfizer has gone down to 12 years of age because we know MIS-C does occur between 12 and 20 years of age. And some recent data has shown that the S protein has super antigen activity. That is it can bind directly to T cells and stimulate a very brisk immune response. So I worry -- I think before we move to children, I think we need a very solid database regarding the safety of this vaccine in older adults. Over.

DR. FINK: Thank you for your questions. So first of all to address the 50 percent point estimate, which, of course, is accompanied by the 30 percent lower bound, we chose those numbers based on a balance of what we thought would be reasonable and feasible to achieve, also taking into account standards that we've used for other vaccines, such as influenza vaccine, and

tried to balance that with what we thought would be needed to actually make an impact. And yes, in a scenario where there are many, many cases of disease, a vaccine that is not strongly effective could potentially still make an impact.

But I outlined a number of reasons why a very weakly effective vaccine could do more harm than good. And the criteria that we came up with we thought were a good balance of both what was feasible and what was necessary to ensure that a vaccine that turns out to be only very weakly protective does not actually get deployed based on a chance finding in a clinical trial. With regards to the flu example that you mentioned, I think it's also important to note that vaccine effectiveness that we see from season to season is based on real world conditions. Our influenza vaccine guidance does specify a lower bound of at least 40 percent or greater than 40 percent for vaccine efficacy to support licensure of seasonal influenza vaccines. And this would be consistent with usual observations

that efficacy point estimates in per-protocol analysis populations in clinical trials tend to be higher than those that we see in effectiveness studies once the vaccine is used in the real world.

In terms of concerns about pediatric development, we do take those concerns very seriously, and I would turn it back to you and maybe other member of the Committee to ask what sort of safety data do you think would be necessary to support progression of pediatric developments, especially down into younger age groups, certainly recognizing that the younger age groups are not the top priority at this time for addressing the pandemic?

DR. MEISSNER: Thank you, yes. I can offer comments. In the paper -- in the *New England Journal* a couple of months ago regarding MIS-C in children in New York state and at a time when SARS-CoV-2 was pretty widely circulating, the rate of MIS-C was two cases per 100,000 children under -- or 100,000 people under 20 years of age. So to me, we've got to be very sure that

these vaccines do not elicit an adverse reaction that may be delayed.

MIS-C seems to be three, four, maybe five weeks afterwards. So I think two months is a reasonable time. But I worry that the vaccines that contain the S protein, which most of them do I think, in genetically predisposed children may elicit a very troublesome reaction. And because disease is generally quite mild -- yes, there are deaths in children. Yes, children do get hospitalized -- do get quite sick. But relatively speaking, it's a very mild disease.

And I think we have to be very sure about the safety of a vaccine in children, and I don't know -- I can't tell you what number would be necessary. It's such a difficult question. But I don't think we can correctly transfer the information that you -- I can't remember if it was you or Dr. Weir said earlier about serobridging. If we get a --

MR. KAWCZYNSKI: Dr. Meissner, I apologize -- and Dr. Fink. We are really running out of time, and

we have to make sure that we get the open session on time. Sorry.

DR. MONTO: Let me make a proposal. Doran, you agreed that we need to discuss this more. Would you be available when we start the Committee discussion later on? Because there were a lot of questions that are still waiting, and we need to move on.

DR. FINK: Absolutely.

DR. MONTO: Very good. Then let's take a ten-minute break, and then we go into the public comments.

[BREAK]

OPENING PUBLIC HEARING

MR. KAWCZYNSKI: -- before I bring the feed back up. Okay, go live, all right. So hold on. All right. Welcome back from our break. I'd like to hand it back to Dr. Monto as we are about to start our OPH session. Dr. Monto?

DR. MONTO: Welcome back and welcome to the Open Hearing Session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the Open Public Hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, and other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If

you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Now over to Prabha.

MR. KAWCZYNSKI: Oh, hold on a second, Prabha, I'll make sure we unmute your phone there. Dr. Atreya, are you there?

DR. ATREYA: Yes. I am here. Can you hear me?

MR. KAWCZYNSKI: Take it away. Yes. we do. Take it away.

DR. ATREYA: Okay. Do I have my webcam on?

MR. KAWCZYNSKI: Yes. You do, ma'am.

DR. ATREYA: Thank you. Good afternoon, everyone. I'm just announcing public speakers, so first we'll go with Ms. Kathrin Jansen. Take away, you have five minutes to talk.

DR. JANSEN: Thank you for the opportunity to speak with you today. My name is Kathrin Jansen, and I'm Senior Vice President and Head of Vaccine Research

and Development at Pfizer. In this position I oversee a global vaccine research and development organization with responsibilities ranging from discovery to registration and post-market evaluation of vaccines to prevent diseases of significant unmet medical need like meningitis B and pneumonia.

I'm here today representing more than 1,000 researchers, clinicians, statisticians, and regulatory experts, and many more colleagues across Pfizer and our partner BioNTech who are working on delivering a potential breakthrough vaccine against COVID-19. We always recognize that safe, effective, and high-quality vaccines are important and now more urgent than ever to provide protection against COVID-19.

To briefly orient you to our COVID-19 program, we have made a conscious decision to evaluate multiple RNA vaccine candidates to address speed of development and the broad immune response to select the one candidate with the best safety, tolerability, and immunogenicity profile. From day 1, we knew that the

selection would be data driven with an emphasis on clinical data. We have been working closely with regulatory authorities, including the FDA, to progress our program while ensuring that safety and maintaining the highest standards in our development process is our top priority.

We have the utmost respect for the FDA and all regulatory authorities and support them in the evaluation of our program. Considering the public health challenge that COVID-19 presents, they are taking a thoughtful approach to regulatory requirements to expedite development without ever compromising vaccine safety or efficacy. Right now the world is looking to science and specifically to vaccines to bring us to the other side of this pandemic.

With increasing levels of public concern about the scientific and regulatory processes to evaluate potential COVID-19 vaccines, I felt it was important to again make clear that science has guided and will always guide our efforts without compromise. We will

never cut corners in our research development or manufacturing efforts to meet any artificial or arbitrary timeline.

Science has overcome disease before and it will again. It is our hope that mRNA vaccines become one of the tools in the fight against COVID-19. We look forward to hearing the discussion today at the FDA VRBPAC meeting. As always, Pfizer and BioNTech will support and meet or exceed the standards for safety, efficacy, and manufacturing that the agency adopts. Thank you so much for your time today.

DR. ATREYA: Okay great. Thank you. We will move on to Ms. Jacqueline Miller.

DR. MILLER: Good afternoon. My name is Dr. Jacqueline Miller, and I'm the head of Infectious Disease Development at Moderna. I'm also a pediatrician who has spent the last 20 years of my career in vaccine development. I've had the privilege of addressing this committee previously, and I'm grateful for the opportunity to speak with you again.

Moderna is developing a candidate vaccine against COVID-19 called mRNA-1273. We've announced that we enrolled 30,000 participants including 15,000 1273 and 15,000 placebo recipients in the pivotal Phase 3 efficacy and safety trial called the COVE study. We want FDA, VRBPAC, and the American people to know that Moderna is committed to rigorous scientific research and the highest quality standards. Transparency is essential to public trust. And that's why we posted our weekly enrollment progress, published our Phase 1 data when available in peer review journals, and we're the first company to post our full Phase 3 study protocol.

While I will not present data from our clinical trials today, I want to spend a moment speaking about messenger RNA or mRNA. This molecule is fundamental to the biology of every cell and serves as a blueprint for all protein synthesis. A vaccine allows cells in our body to activate the immune system in the same way as if we were naturally infected by the

virus but without the potential limitations of administering a live-virus vaccine.

In the case of mRNA-1273 the mRNA sequence instructs the immune cells how to construct the spike protein that naturally occurs on the surface of the virus. These immune cells then learn to recognize the spike protein and develop immune response against it comparable to those seen in those who have recovered from COVID-19.

It's important to note that mRNA does not enter the nucleus, does not interact with a person's genes, and is rapidly degraded by the normal mechanisms the body uses to dispose of its own mRNA. The manufacturing process is cell free, does not use animal products, and does not contain preservatives.

I want to also update you on our development program. Over 25,000 participants have received both doses of study vaccine or placebo. The vaccine was designed in consultation with FDA and the NIH to evaluate Americans at the highest risk of severe COVID

disease. And therefore, 42 percent of study participants are older adults and people with chronic diseases such as cardiac disease and diabetes mellitus.

In addition, our study population represents U.S. demography including communities of color who have been disproportionately impacted by COVID-19. Thirty-seven percent of our study population comes from communities of color, including 10 percent African American and 20 percent Hispanic participants. We're now accumulating data and preparing for study analyses.

As cases of COVID-19 are reported by our study physicians, they're reviewed by an independent safety and data monitoring board or DSMB. Formal efficacy analyses will be triggered when 151 cases have accumulated with two earlier interim analyses after 53 and 106 cases. As we've done throughout this process, Moderna will transparently share the outcomes of these analyses.

While the study is ongoing, the DSMB will continue to monitor the safety of the participants on

an ongoing basis. And ultimately, Moderna will determine whether or not to submit a dossier to FDA requesting Emergency Use Authorization based on an assessment of whether the potential benefit of the vaccine outweighs the potential risks once the required two months of meeting safety follow up have accrued.

We look forward to hearing VRBPAC's recommendations about the handling of potential crossover vaccination for placebo recipients since those participants are beginning to ask when they will know if they received study vaccine or placebo. We intend to continue to generate the data about mRNA-1273 through the Phase 3 protocol and beyond. We're currently planning the initiation of pediatric clinical trials and a collaboration with the National Cancer Institute to evaluate vaccine safety and immunogenicity in patients with cancer. We will also conduct studies to better understand the duration of immunity.

I would like to extend this opportunity to conclude with a heartfelt thank you on behalf of

Moderna to the FDA for their guidance through this process, to our collaborators at the NIH, the COVID-19 Prevention Network, BARDA, and Operation Warp Speed for their intellectual contributions and advice, to our CRO PPD, and most of all to the investigators and study participants who are the true heroes of this endeavor. Without the unselfish dedication of our clinical trial participants, none of this would be possible. Many thanks.

DR. ATREYA: Okay great. Thank you. The next speaker is Dr. David Essayan.

DR. ESSAYAN: My name is David Essayan. I have no conflicts of interest with this topic and no one has paid for my attendance. Given the limited time available and out of respect for the committee and other meeting participants I will limit my comments to a list of considerations for SARS-CoV-2 vaccine development and approval that require additional public discussion. Next slide.

We must consider the mutation rate of the

virus and the risk for escape mutants that may render a spike protein specific vaccine ineffective over time. These considerations include the potential benefits of multivalent- or whole-virus based vaccines and the need for genetic characterization of the virus in clinical trial patients who develop COVID-19 disease to determine whether it matches the vaccine chain sequence or whether it represents a new mutation. Next slide.

We must consider the need for studies assessing long-term safety and efficacy including an assessment for antibody-dependent enhancement and assessment of the efficacy of vaccine in new vaccinees over time to address the concern for escape mutant-mediated loss of efficacy and rigorous pharmacovigilance to assess the duration of protection following vaccination. Next slide.

We must consider the need for post-marketing safety monitoring and reporting specifically addressing the frequently of reports and the need for comprehensive data collection including active

monitoring through a registry for early detection of rare adverse events and serious adverse events. We must also consider the need for an improved understanding of the immune response characteristics necessary for adequate antiviral protection including the role of cell-mediated immunity. Next slide.

We must address the lack of data in children and the need to consider the potential differential safety and efficacy of these hitherto unapproved vaccine technologies on the developing immune system. We must also address the lack of data in pregnant or nursing women, in the advance elderly, and in immune-compromised patients. Next slide.

Finally, we must address the importance of conveying clear, science-based, objective, complete, and accurate data about vaccines to the American public and providing a public response to all questions in order to overcome vaccine hesitancy. We are happy to engage in further discourse on any of these topics. Thank you for this opportunity to address the

committee.

DR. ATREYA: Thank you for your comments. Next speaker is Dr. Annabelle de St. Maurice.

DR. DE ST. MAURICE: Good afternoon, my name is Dr. Annabelle de St. Maurice. And I'm a pediatric infectious disease physician at UCLA. I previously worked at CDC and published on vaccine hesitancy.

MR. KAWCZYNSKI: Actually, hold on one second, Annabelle, hold on one second. Just got to get you set up here. You guys are faster than we are. Hold on a minute. Annabelle, did you have a slide deck?

DR. DE ST. MAURICE: I do not, no.

MR. KAWCZYNSKI: Okay. I'm somehow. Hi, Annabelle, take it away.

DR. DE ST. MAURICE: All right, thanks. Good afternoon. My name is Dr. Annabelle de St. Maurice. And I'm a pediatric infectious disease physician at UCLA and have previously worked at CDC and published on vaccine hesitancy. I have no relevant conflicts of interest and no one has paid for my attendance.

Given my limited time, I would like to focus my discussion on the importance of maintaining confidence in vaccines. This year I personally have seen the erosion of public trust in federal agencies and science. Anecdotally, patients, including healthcare workers, have been refusing influenza vaccine this year due to distrust despite the importance of vaccination during COVID-19.

More than ever we really need to ensure that the vaccine process is transparent and communicated effectively not just in scientific journals but for the general public. The general public needs to understand how a COVID-19 vaccine was approved and understand the process of ensuring vaccine safety. We need to ensure transparency of data, the approval and authorization process, and continued safety monitoring to ensure public confidence in a vaccine.

If a biological license application is not obtained, the reasons for this should be clearly delineated. At a minimum, the FDA must ensure that the

criteria outlined in its October 20th Guidance for Industry on Emergency Use Authorization is met. Disproportionately affected populations including the elderly, African Americans, Latinx, and indigenous populations, and individuals with chronic conditions should be prioritized and represented in clinical trials. This will help ensure public trust and confidence.

We need to get this right to maintain vaccine confidence for future generations. Thank you for your work and for the opportunity to speak to the committee.

DR. ATREYA: Thank you, doctor. Next speaker is --

UNIDENTIFIED FEMALE: I'm sorry. Extension 3102671133 does not answer UCLA voicemail.

DR. DOSHI: Hello? Hello, my --

DR. ATREYA: Dr. Doshi, go ahead.

DR. DOSHI: Hello, my name is Peter Doshi. Hopefully, you can see my title slide now. For identification purposes I --

DR. ATREYA: Yes.

DR. DOSHI: Okay great. I'm on the faculty of the University of Maryland and Medical Journal Editor at the BMJ. I have no relevant conflict of interest and no one's paid for my attendance. A copy of my slides is available on my faculty home page. Next slide, please.

I've reviewed the FDA's guidance on COVID-19 vaccines and the four publicly released Phase 3 trial protocol. My brief talk today aims to point out that unless urgent changes are made to the way the trials are designed and evaluated, we could end up with approved vaccines that reduce the risk of a mild infection but do not decrease the risk of hospitalization, ICU use, or death either at all or by a clinically relevant amount.

The reason for this is that all trials are using a primary endpoint of COVID-19 of essentially any severity such that even a mildly symptomatic person would qualify. For example, in the Moderna and Pfizer

trials, somebody with a mild cough and positive lab test would meet the primary endpoint definition. Next slide, please.

Permitting mild COVID cases to be counted as the primary endpoint will allow trials to complete quickly but doing this will leave us without proof that the vaccine prevents serious complications of COVID. Simply preventing mild cases is not enough and may not justify the risks associated with vaccination. Additionally, without a definitive assessment of efficacy in the elderly and other subgroups at highest risk, we could be left with an approved vaccine that reduces mild cases in healthy people but does little to protect the most vulnerable.

Estimates are that somewhere around half of all deaths are occurring in nursing homes. We need the trials to find out which vaccines can save lives. Next slide, please.

I think this issue has flown under the radar because most people assume severe COVID was what we

were studying. The NIH, in fact, even said so in a press release about Moderna's trial. Next slide, please.

Finally, please note the FDA and sponsor's definition of severe COVID also needs revising because currently, mild COVID-19 cases with the added single criterion of a blood oxygen saturation of 93 percent meets the definition. The problem here is that at least 1 in 20 normal asymptomatic older adults have an oxygen saturation of 92 percent or less. Low blood oxygen levels are arguably an important risk factor for severe disease, but they are not severe disease itself.

MR. KAWCZYNSKI: Thirty seconds.

DR. DOSHI: Next slide, please.

Most Americans assume our vaccine development process in contrast to, say, Russia's ensures that an approved vaccine can save lives, reduce hospitalization and ICU admission. But unless we set the right primary endpoint in trials, we won't have hard evidence to know that is the case. Thanks for listening, and I'd be

happy to take any questions.

DR. ATREYA: Okay great. Thank you for your comments. Dr. Kaplan, Robert Kaplan.

DR. KAPLAN: Hi. I'm Robert Kaplan. I am a faculty member at the Clinical Excellence Research Center at Stanford University. I'm also a former NIH Associate Director with responsibility for overseeing the Behavioral and Social Sciences programs across the NIH institutes and centers. And I'm also a former Chief Science Officer at AHRQ. I have no conflicts of interest, and nobody paid for my attendance.

I want to talk to you today about vaccine hesitancy. Although there are a lot of nuances in seroprevalence studies, current estimates from Stanford suggest that only about nine percent of U.S. population have neutralizing antibodies or about 91 percent of the population may be at risk. As has been mentioned several times today, if a vaccine is about 50 percent effective and the uptake rate is only about 50 percent, then about 75 percent of the population might remain

unprotected. We're all in this together.

Recently our center has been doing a series of public opinion surveys in collaboration with YouGov. Our most recent study that was completed around the 1st of April showed that only about 35 percent of the U.S. population reported being very likely to take a vaccine with another 29 percent saying they're likely to take a coronavirus vaccine. A full 1 in 5, or 20 percent of the U.S. population suggest they would not take a vaccine under any circumstances.

And in response to another question, about 36 percent of the U.S. population endorsed the statement that said it's definitely or probably true that vaccine harmful effects are not being disclosed to the public.

Next slide. I think I missed a few transitions. So we should be on the slide that shows a series of blue bars and histograms.

We know that the percentage that are likely to take the vaccine systematically increases with age. I'm sorry, with education, with those completing more

years of formal education being the most likely.

But one of the findings -- next slide -- that has been reported less often is that the variables that we find most influential are not necessarily demographic variables but in fact are political ideologies. Our studies show that those who describe themselves as very conservative and less trustful of government are least likely to say they would take a vaccine.

I also want to point out --

MR. KAWCZYNSKI: Thirty seconds.

DR. KAPLAN: -- next slide -- that our results are quite consistent with a variety of other polls. And this study from Bracken, for example, also shows systematic declines in likelihood of taking vaccine just over the last six months. Next slide.

So in conclusion the Stanford/YouGov data shows increasing skepticism about a coronavirus vaccine. And this hesitancy has been accelerating over the last few months. We believe that rushing an

approval or an EUA could increase skepticism. There may be long-term consequences of a decision that precedes the evidence. So what can we do? Well, first of all as has been mentioned several times today, more transparency --

MR. KAWCZYNSKI: Time has come up.

DR. KAPLAN: -- and inclusive discussions that go beyond traditional demographic variables. And finally, we're in this together. We need to achieve high vaccine participation through assurance that there have been no shortcuts in establishing safety and efficacy. Thanks for having me today.

DR. ATREYA: Okay great. Thank you and next speaker is Mr. Kermit Kubitz.

MR. KUBITZ: Hello. My first slide says what is a good coronavirus vaccine looking at it from overall public health and personal safety choices. Next slide.

I'm 73 years old. In 1954 I was a polio pioneer in the Salk vaccine trial. Next slide.

The objectives of COVID-19 vaccination should be to protect widely, public health through both direct protection and indirect protection. Next slide.

My objectives are what is my dominant anti-infection personal strategy? So far, I've been masking, shopping once a week, social distancing. When would a vaccine change that?

COVID vaccine -- next slide -- COVID vaccine evaluation is proceeding under an emergency use paradigm with safety from 30,000 participants studies. But it must be followed by effectiveness studies. Emergency Use Authorization with a benefit-risk ratio is appropriate, but future vaccines should also get the benefit of EUA if early vaccines have less than 80 percent effectiveness.

Efficacy is preliminary analysis. Effectiveness is -- next slide -- effectiveness is protection in mass use, which would inform the public and the community about how well vaccines work. Efficacy and vaccine uptake, as other people have

commented, interact. Next slide.

Efficacy objectives of 50 percent may be affected by the number of degrees of freedom. That is what if the placebo has 200 cases and the vaccinated trial has 50 cases, but that's affected by non-pharmaceutical interventions like masking and distancing, and would be 100? You don't know that until the masks and the social distancing come off. Next slide.

So I need to know if a vaccine is 65 percent effective, is it working for me? I recommend consideration of innovative serology techniques. I have no connection with Adaptive Therapeutics, but I recommend their consideration of T-cell response. And so I thank you for your consideration but follow up is definitely limited. Thank you very much. Bye.

DR. ATREYA: Okay great. Thank you so much. The next speaker is Dr. Andy Pavia.

DR. PAVIA: Yes, thank you Dr. Monto and thank you colleagues. I'm Dr. Andrew Pavia, and I'm Chief of

Pediatric Infectious Diseases at the University of Utah representing today as a member of the HIV Medicine Association which is part of the Infectious Diseases Society of America. I have no relevant conflict of interest, and no one's paid for my travel, which would be a trick over Zoom.

Thank you for the opportunity to offer comments regarding the FDA's consideration, the application, and for sharing the guidance and the transparency that you've shown. HIVMA and IDSA would prefer that COVID-19 vaccines be approved through a BLA or Biologics License Application with the high standards that that would entail given the importance of ensuring the safety and the efficacy of a vaccine that is going to be given to hundreds of millions of healthy people.

At a minimum, the FDA should ensure that the criteria outlined in its October 20th guidance be met including a full analysis of at least two months of safety and efficacy data and that the point estimate of

60 percent efficacy that Dr. Marston specified be the specified endpoint.

Wide acceptance of COVID-19 vaccines will be critical to achieve vaccination rates which are necessary to stop the spread of SARS-CoV-2. As we have heard, many times without high uptake no matter what the effectiveness of the vaccine is, there will be no effectiveness in stopping the pandemic. Therefore, we strongly recommend that a vote of support by FDA's Vaccines and Related Biological Products Advisory Committee be required before FDA consider an authorization or a formal approval.

Transparency is, of course, critical to building trust among the public but also among the medical community. Most patients trust their own provider. Therefore, we feel that -- critical for FDA to share trial data with CDC's Advisory Committee on Immunization Practices prior to authorization or approval. The ACIP is a source that most practitioners trust and turn to for advice.

Due to varied endpoints across the vaccine studies in different sponsors, it will be important for the FDA and for VRBPAC to evaluate and compare standardized endpoints to include severe disease and using standardized analyses across the vaccine candidates in a manner similar to what FDA has pioneered for FDA -- for HIV therapeutics. In addition in considering a BLA or an EUA, clinical trial efficacy must be available at the time of decision on the efficacy of the vaccine candidate in the populations who have been most impacted by COVID-19 including the elderly, African Americans, Latinx, and indigenous populations.

MR. KAWCZYNSKI: Ten seconds.

DR. PAVIA: Lastly, if a vaccine is made available through an EUA, FDA must ensure a strategy to continue the collection of blinded data after the issuance of an EUA. We're concerned that the practical and ethical issues will make it difficult to do this, and that's one more reason that a very high standard

needs to be met, not the minimal legal requirement for an EUA. Thank you very much for the opportunity to provide input and thank you for the work that you're all doing.

DR. ATREYA: Great. Thank you so much. The next speaker is Dr. Marcus Schabacker.

DR. SCHABACKER: Good afternoon. I'm an physiologist and internist, and affiliated associate professor at the Stritch Medical School of Chicago, and the President and CEO of ECRI. And on ECRI's behalf I'm speaking today to you. Thank you for inviting me. I have no conflict of interest, financial or otherwise, to report.

ECRI, a trusted voice in healthcare, is an independent, non-for-profit organization. Our mission is and has been for over 50 years to advance effective evidence-based healthcare globally. Next two slides, please.

We are here today with an urgent call for the review of completed clinical trial data to ensure the

safety and effectiveness of COVID-19 vaccines, a paramount consideration for understanding the risks and benefits of any of the vaccines under development. ECRI fears that unexpected events may occur if a vaccine is rolled out with rushed timelines and incomplete data. Vaccine trials can fall short of their aim because trial conditions are highly controlled and may not reflect real-world conditions and outcomes, especially now with so many unknowns about the coronavirus.

Considering preliminary trial data for rapid vaccine development deployment can introduce additional risks of bias substantial enough to invalidate the evaluation and therefore, might not be justified even in the context of a pandemic. We ask the public and regulators and the expert committee to be mindful of three key points.

Operation Warp Speed trials are well designed and should provide robust data but only if completed as designed. Preliminary trial data are inherently

unreliable and should not be used to support action when there's risk of harm.

Number 2, it is imperative that the first vaccines distributed in the U.S., and we have heard that numerous times today, be safe and effective or we will risk losing the public's already diminished trust needed to control the spread of the virus. Deploying a safe but weak COVID-19 vaccine may actually worsen the pandemic if other public health measures are relaxed.

And number 3, as a science-based, patient safety organization, we respectfully disagree with Dr. Fink and the FDA and appeal to you to demand a minimum of six months follow up from the full trial cohort before EUA is considered. To control COVID-19, immunization must be conveyed to more than 50 percent of recipients and provide protection for at least six months to be useful in reducing the virus spread.

Follow up of at least six months is necessary to understand the risks, of inadequate exposure and waning immunity, to enrolled patients. Furthermore,

interim analysis at earlier points is at risk of bias such as demographic sampling imbalance as mentioned earlier today by NIH Dr. Marston. Next slide.

After reviewing the limitations of COVID-19 vaccine testing and the potential harms that vaccines might cause, ECRI recommends COVID-19 vaccine deployment only after thorough review of completed Phase 3 trial data. And under no circumstances should vaccines be authorized with fewer than six months of follow up data from the full trial cohort.

MR. KAWCZYNSKI: Time's up.

Additionally, we urgently ask for post-authorization comprehensive surveillance trials such as discussed earlier today for all vaccinated individuals. Doing any less would simply risk too much and the consequences might be severe. Thank you for your time. Thank you.

DR. ATREYA: Thank you. Thank you for your comments. The next speaker is Dr. Sidney Wolfe.

MR. KAWCZYNSKI: Dr. Wolfe?

DR. WOLFE: Yes.

MR. KAWCZYNSKI: Go ahead, Dr. Wolfe. Are you there?

DR. WOLFE: Yes.

MR. KAWCZYNSKI: Go ahead.

DR. WOLFE: I'm Sidney Wolfe, Dr. Sidney Wolfe of the Public Citizen Health Research Group. I have no financial conflicts of interest. Next slide.

Although there have been some recent additions to what's required for Emergency Use Authorization, they're still grossly inadequate. EUA efficacy standard is now potentially 50 percent or greater significant reduction of COVID-19 in vaccinated compared to placebo cases as it is for vaccine approval. And as you've heard before, EUA standards for chemistry manufacturing controls are now closer to those required for approval. But how much longer after the currently inadequate EUA requirements could be fulfilled would it take to complete the all-important Phase 3 trials and for FDA and your advisory committee

to review the data?

These are just two major reasons why the currently allowable deficiencies impair any legitimate benefit-risk evaluation. You've heard this before, but phrased in a starkly different but accurately way, EUA approval could occur when up to half of the participants in Phase 3 trials have been followed for less than two months after completion of full vaccination.

Safety data would include over 3,000 vaccine recipients. This is out of between 15,000 and 30,000 in various trials followed for serious adverse events and adverse events of special interest for little as one month after completion of vaccination.

The benefits, obviously, of using unfinished Phase 3 data are faster availability of the vaccine depending on how much time beyond whenever the EUA is filed or is able to be filed now to finish Phase 3 studies. The risks are obviously incomplete safety and efficacy data because large Phase 3 studies have not

been finished and reviewed by the FDA and your committee.

Saving time by faster but riskier data deficient EUA pathway will surely be outweighed by the loss in public confidence in an incompletely tested, unproved EUA vaccine accompanied by decreased willingness to be vaccinated. So the question for the advisory committee is, I think, straightforward. Based on incomplete Phase 3 trials, will your advisory committee -- and we're getting into confidence in this case of that of the advisory committee members. Based on your Phase 3 trials, will your advisory committee have enough confidence despite all this missing data to recommend authorizing, by an EUA, a vaccine for use in tens of millions of people? The gap between completed Phase 3 trials needed for approval, and the current EUA standard exemplified by allowing half of Phase 3 trial participants to be followed for less than two months after vaccination, does not engender confidence. Thank you very much for the opportunity to speak with you

today.

DR. ATREYA: Thank you so much, Dr. Wolfe. The next speaker is Dr. Diana Zuckerman.

DR. ZUCKERMAN: Thank you. Are my slides up?

DR. ATREYA: Yes.

MR. KAWCZYNSKI: Yes, ma'am.

DR. ATREYA: Yes. Go ahead.

DR. ZUCKERMAN: Thank you. I am Dr. Diana Zuckerman, President of the National Center for Health Research. Next slide. We scrutinize the safety and effectiveness of medical products, and we don't accept funding from companies that make those products though I've personally inherited stock in J & J.

My expertise is based on post-doctoral training in epidemiology and as a faculty member and researcher at Vassar, Yale, and Harvard. I've also worked at HHS, the U.S. Congress, and the White House. Next slide.

We've heard that the agencies are doing many things right. But the vaccine trials have serious

design flaws. The standards set in FDA guidance and the study protocols make it likely that vaccines that will be authorized or approved won't achieve what the public and policy makers expect. Instead, these vaccines will only be proven to reduce the risk of mild infections but not proven to reduce the risk of hospitalization, ICU, or death.

The major flaws are as follows. The FDA's proposed primary endpoint is defined as symptomatic COVID-19 that can include only one very mild symptom such as a mild cough or sore throat as long as the person has tested positive. The FDA's requirement of at least two months median follow up after vaccination or a placebo is too short to study efficacy. Even if a person is exposed during that time, we don't know the correlates of protection and so we need a longer follow up to know how long an effective vaccine remains effective.

We can't rely on post-market studies for that information because once a vaccine is on the market,

many people in the placebo-controlled group will switch to a vaccine. And we don't know whether diversity of study participants will be achieved in terms of age, race, or comorbidities, especially for those people who are exposed to the virus. Next slide.

The requirement of at least five serious COVID-19 cases in the placebo group is completely inadequate for two reasons. Serious COVID-19 cases are too loosely defined and could include a case of mild COVID-19 if the patient has a blood oxygen saturation under 93 percent.

But thousands of otherwise healthy Americans have levels below that. And even if the definition were more stringent, such as requiring hospitalization or death, and even if there were no such cases among the vaccinated patients, the absolute difference in disease between zero and five serious cases would not be clinically meaningful to individuals and could easily have occurred by chance.

Next slide. The next one just shows the FDA

guidance, so let's skip that and go to the last slide.

In conclusion, the last slide with bullets, I should say. The American public has been told that life can go back to normal when we have a vaccine. It isn't FDA's job to achieve that overly optimistic goal for any vaccine, but it is FDA's job to make sure that a vaccine --

MR. KAWCZYNSKI: Time.

DR. ZUCKERMAN: -- has meaningful benefits for the health and lives of most Americans and especially those most at risk. Thanks very much.

DR. ATREYA: Thank you for your comments. The next speaker is Dr. Jeffrey Duchin.

DR. DUCHIN: Good afternoon. I'm Dr. Jeff Duchin, Health Officer for Public Health Seattle and King County in Washington, and Professor in Medicine at the University of Washington. I'm speaking today as a member of the board of directors of the Infections Diseases Society of America. I have no relevant financial relationships, conflicts, and no one has paid

for my participation.

The Infectious Disease Society, IDSA, prefers COVID-19 vaccines be approved through the traditional Biologics Licensure Application. Short of that, FDA must ensure that the criteria outlined in its October 20th Guidance for Industry on Emergency Use Authorization are met, including full analysis of at least two months of safety and efficacy data following the last dose.

Public trust is critical to build vaccine confidence and for successful uptake of COVID-19 vaccine. Therefore, we strongly recommend that public deliberations and a vote of support by FDA Vaccines and Related Biologics Products Advisory Committee, VRBPAC, be required before authorization or licensure. IDSA emphasizes that clinical trial data on the use of a vaccine candidate with the populations who have been most impacted by COVID-19 must be available for BLA or EUA consideration. These populations include the elderly, Black, Latinx, indigenous people, and those

with chronic conditions.

Transparency is critical to building trust among the public and the healthcare providers that the public will look to for advice on vaccination. We urge FDA to share vaccine trial data with CDC's Advisory Committee on Immunization Practices as soon as it is available to VRBPAC and prior to a decision on authorization or licensure.

The ACIP is the trusted authority that provides guidance on vaccines to our nation's healthcare providers. Their review and recommendations to healthcare providers regarding populations to be vaccinated, equity, and implementation considerations will be critical to a successful vaccination program.

Before making COVID-19 vaccine available through an EUA, FDA must ensure the trial sponsor has outlined a feasible strategy for continuing the vaccine trial post-authorization given the challenges continuing a trial after a product is available for public use. And due to the novel vaccine platforms and

technologies being considered, we also recommend manufacturing facilities be inspected as part of the process of approving or authorizing a vaccine for COVID-19.

And finally, IDSA would like to remind everyone that even after a COVID-19 vaccine is available, other COVID-19 prevention measures including masking, physical distancing, improving ventilation, and handwashing will remain critical as vaccine uptake increases and we learn about long-term protection. Thank you for the opportunity to provide input on the approval or authorization of a COVID-19 vaccine needed to protect both Americans and person worldwide.

DR. ATREYA: Okay. Thank you so much, Dr. Duchin. Our next speaker is Elizabeth Battaglino.

DR. BATTAGLINO: Hi, good afternoon. I'm Beth Battaglino. I'm a practicing fetal and maternal health care provider and President and CEO of Healthy Women, the nation's leading nonprofit health organization representing more than 18 million women. We provide

consumers and healthcare providers accurate, evidence-based information about diseases and conditions, innovations in research and science, and changes in policy that affect women's access to treatment and care. I come before you today to talk about the need for public trust in vaccine research and the need for any approval to report sex differences.

The development of COVID-19 vaccine is our best hope of ending this deadly pandemic. Vaccines save millions of lives every year but only if people have access and are willing to get vaccinated.

A recent survey from STAT and The Harris Poll revealed that 78 percent of Americans worry that the COVID-19 vaccine approval process is being driven by more politics than science. In September, Pew Research found that only 21 percent of respondents would definitely get a vaccine if it were available immediately down from 42 percent in May. Public trust in science and information from our federal agencies has been undermined.

It is therefore imperative that we address the spread of misinformation and the growing fear and distrust of the regulatory process and its politicization. That agencies must show that any approval and distribution of vaccines is a result of vigorous regulatory review such as independent data and safety monitory boards and a panel of outside scientific advisors that find that vaccine safe and effective.

With respect to research, it's crucial that sex differences be analyzed and reported along with approvals for COVID-19 vaccines. It is established that there are sex differences in immune functions and responses to vaccination. Women build better immunity to infections compared to men due to estrogens and certain genes on the X chromosome which cause lower viral loads, less inflammation, and higher levels of antibodies that remain in circulation longer. Research on influenza vaccines has demonstrated that women only need half the usual dose to get the appropriate immune

response.

The FDA should determine whether women report greater adverse events or side effects more often or to a greater extent than men since women are known to generate stronger antibody responses to viruses. To that end, women and men should be equally represented in the clinical trials, and the data should be disaggregated for analysis.

We believe implementing these recommendations will ensure the success of COVID-19 vaccines. Thank you for the opportunity to present today.

DR. ATREYA: Okay. Thank you so much for your comments. The next speaker is Dr. Arthur Caplan.

MR. KAWCZYNSKI: Dr. Caplan was unable to stay on.

DR. ATREYA: Oh, okay. So we will move to the next speaker then. Next speaker is Ms. Sarah Christopherson.

MS. CHRISTOPHERSON: Hi, thank you. My name is Sarah Christopherson. I am the Policy Advocacy

Director at the National Women's Health Network. We're a nonprofit advocacy organization that has been bringing the voices of women to the FDA for 45 years. We are supported by our members, and we do not accept financial support from drug or device makers. And I have no conflicts of interest to disclose.

As we heard earlier in the powerful Reagan-Udall presentation this morning, there is a larger sociopolitical context for today's meeting. The ramifications mean you must go above and beyond before recommending EUA. As noted in several presentations, distrust of even widely used vaccines predates the pandemic and has only grown this year. Meanwhile, the President of the United States has promoted unproven miracle cures and dangerous theories for partisan gain. Added to that volatile mix, FDA has made serious missteps this year.

And while we recognize that FDA resisted shortcutting the collection of follow up data in the face of significant external political pressure, much

damage to public trust has already been done to the public's faith in federal scientific integrity. This committee must play a strong role in reassuring the public that the vaccine is safe and effective. Otherwise, the damage could ripple through public health for decades.

Relatedly, while the guidance strongly encourages clinical trial enrollment of the populations most affected by COVID-19, we urge this committee to go further and not recommend an EUA until there's sufficient data to demonstrate that the vaccine works in those groups who are most affected. As noted earlier today, Black, Latinx, indigenous, and other people of color have faced high and disproportionate infection and mortality rate.

They've also expressed a strong interest in knowing that the vaccine will work in people like them. Yet they are significantly underrepresented in vaccine trials, and there's no guarantee that they will be included in case-driven interim analyses.

Determining safety and efficacy in a clear and compelling manner must mean more than simply reaching a sufficient number of total cases. The sponsors' protocols indicate that they will take an interim look at the effectiveness of their vaccines at 31 or 53 cases. While that might be enough to demonstrate that s vaccine is effective overall, we believe that the committee should ask for more.

Do those cases show that the vaccine is effective in women, in people of color, in older adults? No matter how many cases have occurred in the vaccine trials when the committee is finally asked to weigh in on a sponsor's data, communities of color, women, and older adults must have confidence the vaccines work for people like them.

MR. KAWCZYNSKI: Time's up.

MS. CHRISTOPHERSON: We're counting on you to send a strong message to the FDA. Thank you for your consideration.

DR. ATREYA: Great. Thank you so much for

your comments. The next speaker is Ms. Lynda Dee.

MS. DEE: Hi, I'm from AIDS Action Baltimore in the --

DR. ATREYA: Linda Dee?

MS. DEE: Yes?

DR. ATREYA: Go ahead. Go ahead, please.

MS. DEE: Can you hear me?

DR. ATREYA: Yes. Go ahead, please. Thank you. Go ahead. Ms. Dee, can you hear me? Please go ahead and make your remarks, please.

MR. KAWCZYNSKI: Ms. Dee, did you mute your own phone?

MS. DEE: Can you hear me now?

MR. KAWCZYNSKI: Yes. Now we can hear you. Go ahead, Ms. Dee.

DR. ATREYA: Yes.

MS. DEE: Okay. All right, sorry. I'm from AIDS Actin Baltimore and the AIDS Treatment Activist Coalition, a former CBER Antiviral Advisory Committee community representative. I'm delighted that the

agency did an end run around the White House when it publicized today's briefing document which resulted in OMB approval of the new vaccine guidance.

The HIV community applauds the agency's courage and battle for scientific integrity, especially the center directors who published in USA Today. But we all know that anything can happen with this administration at any time. That's why you need to advance the agency's bravery and determination. You are the last bastion of independent U.S. scientific experts able to prevent or help to prevent dangerous politicization of science and ensure public protection against authorization or licensure of COVID vaccines.

Plus I would urge you consider the following recommendations that are more stringent than the new FDA guidance. We need to establish adequate safety and efficacy if we wish to -- if not, we will do more harm than good and we could really crash the vaccine effort for years to come.

We need to require that in future vaccine

trials a significant number of older adults and people of color are included to permit a safety and efficacy sub-analysis for these populations as well as their comorbidity. If there are insufficient numbers in current Phase 3 trials to permit a sub-analysis, describing acceptable risk-benefit analysis that would justify an EUA and require post-marketing studies that will establish safety and efficacy. Recommend that adequate funds be allotted for government community advisory boards and industry community advisory boards constituted with COVID-19 survivors and advocates to foster education and inclusion of these vulnerable populations.

Tuskegee is always foremost in the minds of African Americans. They do not trust the government or industry. The Reagan-Udall comments clearly prove we still have a lot of work to do before communities of color are going to volunteer for a vaccine or any other COVID-19 trial. Recommend that the Phase 3 trial vaccines include people with controlled HIV, HPV, HCV,

and other important comorbidities and require a pathway for the inclusion of pregnant women. Recommend a 75 percent standard to promote vaccine confidence.

Require that participants be followed for three to six months not just two months, to provide adequate time to capture most usual serious adverse events. Recommend that all Phase 3 participants be followed for at least one year after EUA or licensure to establish durability and long-term safety. Recommend BLA not EUA after VRBPAC approval. Thank you for your dedicated commitment and service and for allowing me to comment.

DR. ATREYA: Thank you so much Ms. Dee. The next speaker is Ms. Claire Hannan.

MS. HANNAN: Hi. Can you hear me?

DR. ATREYA: Yes, very much so. Thank you.

MS. HANNAN: Okay, great. Thank you. Good afternoon. I'm Claire Hannan, Executive Director of the Association of Immunization Managers. I don't have any specific conflicts but AIM as an organization does

accept educational grants and contributions from corporate entities.

AIM represents the 64 immunization awardee jurisdictions, 50 states, 8 territories or federated states and 6 large cities. They have all submitted vaccine distribution plans to CDC. So the states are working very hard to prepare for potential distribution of a vaccine, but the distribution plans will only be successful if people show up and accept the vaccine. And this will only happen if we establish trust and confidence in the vaccine.

Because the turnaround time from potential EUA authorization to vaccine distribution is very short, it's critically important that trust in the approval and authorization process be established early and maintained throughout the process. The guidance provided by FDA for vaccine licensure and the additional guidance for the EUA is extremely helpful. It's also extremely reassuring that VRBPAC will meet and will review data and make recommendations on EUA as

well as licensure. We're very thankful for these measures.

The transparency continues to be critically important. Holding open online meetings allow the public to see for themselves how the process works. Thank you for making this meeting accessible to the public. We encourage you to continue to be transparent with all of your actions. We encourage the FDA to produce and distribute educational materials targeted to specific communities and at low literacy levels.

By reassuring the public that the vaccine approval process is conducted ethically, transparently, without interference, and through a health equity lens, VRBPAC can help build confidence in the safety and efficacy of any approved or authorized COVID-19 vaccine. The committee and FDA must continue to openly inform the public about the progress of the vaccine trials and post-approval safety monitoring.

Beyond the COVID-19 vaccine, VRBPAC plays an essential role in recommending approval of vaccines and

biologics. Parents and consumers trust this process knowing that independent experts on VRBPAC thoroughly review all related data. It's critical that the trust in the scientific review be preserved. Any deviation from this process could erode trust not only in COVID-19 vaccines --

MR. KAWCZYNSKI: Ten seconds

MS. HANNAN: -- but also in routine vaccinations as well. We thank the members of the VRBPAC committee for their time and expertise and commitment. Thank you so much.

DR. ATREYA: Excellent. Thank you so much for your comments. The next speaker is Ms. Elizabeth Lovinger.

MS. LOVINGER: Yes.

DR. ATREYA: Go ahead, please. Go ahead and make your comments.

MS. LOVINGER: Hello. My name is Elizabeth Lovinger. I'm a Senior Government Relations and Policy Officer at Treatment Action Group. And I have no

relevant conflicts of interest to declare. Thank you for the opportunity to comment on behalf of Treatment Action Group. Our comments and recommendations encompass a broad range of community concerns regarding COVID-19 vaccine development and regulatory review as follows.

Number 1, there have been unprecedented missteps and misstatements related to Emergency Use Authorizations for hydroxychloroquine and convalescent plasma for COVID-19, and it is vital that similar debacles do not occur with vaccines. This is a particularly important concern when vaccine hesitancy in the U.S. is rising, as was noted in today's meeting, with only 50 percent of the American public trusting any COVID-19 vaccine candidate approved by the FDA. The agency can restore public trust by improving transparency and communication and by removing staff who have been involved in perpetrating political interference.

Number 2, we appreciate the issuance of FDA

guidance on EUAs for COVID-19 vaccine candidates. However, we strongly recommend that the parameters outlined should be viewed at the absolute minimum requirements particularly for duration of safety follow up. Number 3, the unprecedented speed at which prospective COVID-19 vaccines are being developed point to the need for post-marketing surveillance to be required and strongly enforced by the FDA.

Number 4, robust information should be obtained on safety and, if possible, in subgroup analyses, efficacy of COVID-19 vaccines in survivors of tuberculosis and people living with HIV and other chronic viral infections, including but not limited to hepatitis B and C. Number 5, vaccine developers should generate data on safety and efficacy across the full age spectrum in women, transgender and gender nonconforming people, and men, and in racially and ethnically diverse population.

Number 6, in addition to being transparent with data on people who become pregnant during efficacy

trials, authors should be asked to disclose plans and timelines for the developmental and reproductive toxicology work necessary to conduct clinical research specifically in pregnant and lactating people. Similarly, sponsors should disclose plans and timelines for the clinical research necessary to obtain vaccine licensure in pediatric populations.

Number 7, the FDA must ensure that COVID-19 vaccine efficacy evaluations proceed for sufficient duration to obtain evidence on the duration of immunity if vaccine-mediated protection from SARS-CoV-2 infection and/or COVID-19 disease is demonstrated. Number 8, we encourage the FDA to proactively consider the implications for ongoing and future efficacy trials if and when a vaccine safely meets or exceeds the 50 percent efficacy threshold for approval. Issues will arise regarding how to approach control arm and trial design. And this may be an appropriate topic for an additional FDA guidance document.

Finally, number 9, sponsors should be

encouraged to monitor for potential cases of re-infection with SARS-CoV-2 among trial participants. Trials also offer the opportunity to evaluate the effects of pre-existing immune response to seasonal coronaviruses on the response to vaccination, SARS-CoV-2 infection, and COVID-19 disease. Making the samples available to independent researchers would allow important questions on these topics to be addressed.

Lastly, we encourage you to refer to our fuller written comments for further information and explanation. Thank you.

DR. ATREYA: Okay great. Thank you. The next speaker is Dr. Peter Lurie.

DR. LURIE: Good afternoon. I'm Peter Lurie, President of the nonprofit Center for Science in the Public Interest and an Associate Commissioner at FDA from 2014 to '17. I have no conflicts of interest to disclose.

This meeting represents a potential turning point in assuring that the scientific method and the

principle of transparency take center stage. Until now, the process of developing candidate vaccines has been inappropriately politicized with an eye on the election calendar rather than the deliberate timeframes that science requires. Now is the time for a reset. This committee has a unique opportunity to set a new tone for vaccine deliberations going forward.

In so doing, the following five principles should be honored. One, agency transparency. The committee must assure that FDA honors its commitment to hold an advisory committee meeting on particular products before issuing EUAs. The committee should also pressure the agency to provide more detail on the reasons for clinical holds on vaccine trials and on other products.

Two, corporate transparency, while some companies have released their clinical trial protocols, others have not. And in general, companies have not provided detailed statistical analysis plans or stopping rules. This committee should also insist that

companies granted EUAs commit to rapid submission of BLAs.

Three, appropriately high efficacy standards. FDA has been inconsistent in its application of EUA standards during the course of this pandemic, often accepting data considerably weaker than it has in previous emergencies. When a vaccine candidate comes before this committee, I urge you to interpret these efficacy standards rigorously. The vaccine that is only minimally effective is one for which any efficacy can be overwhelmed if people lowering their guards and reduce mask wearing or social distancing.

Four, high safety standards. Even for authorized products it is critical that sponsors continue to follow subjects for up to a year to monitor for late-occurring adverse events and to establish whether immunity wanes. This committee should also seek clarity on the agency's efforts to exclude vaccine-induced enhanced respiratory disease. Even after today's presentation, I remain confused about the

EUA guidance and how it suggests that there should be at least five placebo subjects who should have severe COVID disease.

Five, high ethical standards. This committee should demand that informed consent forms and institutional review board minutes be made public. It should assure that subjects are receiving proper counseling on how to avoid infection with SARS-CoV-2 and that vaccines prove truly safe and effective are provided to control patients in ongoing and subsequent trials.

The politicization of vaccines in this pandemic has already undermined public trust contributing to an alarming rise in vaccine hesitancy. A vaccine that is --

MR. KAWCZYNSKI: Fifteen.

DR. LURIE: -- not accepted is an ineffective vaccine. The only anecdotes to public mistrust are scientific rigor and transparency. I urge the members of this committee to be their staunchest advocates.

Thank you.

DR. ATREYA: Thank you so much, Dr. Lurie. The next speaker is Ms. Emily Martin.

MS. MARTIN: Hello, good afternoon, and thank you for the opportunity to address the committee. I have no relevant conflicts of interest to disclose. My name is Emily Martin, and I am an Associate Professor of Epidemiology at the University of Michigan School of Public Health. I'm an infectious disease epidemiologist. And my research and public health practice involves studying the effectiveness of vaccines and how vaccines can be used broadly to protect as many people as possible.

Today I am advocating that Emergency Use Authorization should only be applied to limited situations and that EUAs must not preclude the completion of ongoing randomized trials. The standards for an EUA must be high and EUAs must be applicable only to limited populations with the highest level of exposure, including healthcare workers or first

responders.

Before making a COVID-19 vaccine available through an EUA, the FDA must ensure that the trial sponsor has outlined a feasible strategy for continuing the trial after the authorization. Data from randomized control trials are essential for laying the groundwork needed for vaccine policy going forward. These trials must prioritize the inclusion of those experiencing disparate impacts of the pandemic to date. Importantly, these trials must be continued until their completion in order to gather the data that's needed to protect these groups.

Without complete and full randomized trial data, we will lack the evidence base needed to monitor and adapt to vaccination strategies as needed over the many years that these vaccines will be in use. The complexities of vaccine effectiveness monitoring are particularly challenging when multiple products and vaccine platforms are available as could be the case with COVID-19 vaccines. For this reason it is

essential that all trials are continued until completion.

It is too soon to know the details of how the coming COVID-19 vaccines will need to be delivered. As we learned with the influenza vaccine, post-distribution studies will be needed and will be critical to continually refine when and how often to administer the vaccine and to identify those groups in need of additional strategies for protection. However, post-distribution and comparative effectiveness studies must be founded upon robust randomized trial data. And ending these trials early will irrevocably hamper our ability to optimize the effective use of the vaccine going forward.

Thank you again for the opportunity to speak to the committee today. And thank you for your important work.

DR. ATREYA: Great. Thank you so much, Dr. Martin. Next speaker is Ms. Susan Peschin.

MS. PESCHIN: Hello, I'm Sue Peschin,

President and CEO of the Alliance for Aging Research. The Alliance receives industry funding for non-branded older adult vaccine and COVID-19 education, but we have no conflicts for this meeting.

It is hard to comprehend the horror of mass COVID-19 deaths among those age 65 and older in the U.S. totaling more than 160,000 people. That's 80 percent of all COVID-19 related deaths in a group that only accounts for 16 percent of the U.S. population. Please keep that in mind as you do your work.

First, research shows our immune systems grow weaker as we age. This phenomenon, known as immunosenescence, makes the immune systems of older adults less responsive to standard vaccines. Thankfully, there are FDA approved enhanced flu vaccines specifically designed for older adults that help overcome the effects of immunosenescence.

Unfortunately, in their most current recommendations, the CDC's Advisory Committee on Immunization Practices or ACIP once again avoided

recommending enhanced flu products over standard dose for those ages 65 plus. This was a missed opportunity to encourage older adults to better protect themselves during the worst pandemic in 100 years. Yes, any flu shot is better than no flu shot, but older adults need all the protection they can get. So it's critically important to understand geriatric immune response as you review COVID-19 vaccines.

The Alliance implores the FDA and VRBPAC to be transparent about all steps taken to ensure COVID-19 vaccines are safe and effective for older adults, particularly those 80 and older. Sponsors should be required to explicitly demonstrate how their vaccines were tested and how they performed among stratified older age groups in late-stage trials. And because COVID-19 vaccines may be granted EUA status, we strongly advocate the FDA require public reporting of post-market studies.

Second, it makes sense public health experts are recommending that those in nursing homes be among

the first groups to receive a COVID-19 vaccine. However, we ask the FDA, VRBPAC and ACIP to consider which COVID-19 vaccines will provide the most protection to our oldest citizens and balance it with efforts to prioritize distribution and administration.

Third, COVID-19 vaccines will be considered for EUA during flu season. The FDA's thinking on COVID-19 vaccines and co-administration with flu or other CDC recommended adult vaccines is very important. We urge you to make this information a priority in provider and patient education efforts.

MR. KAWCZYNSKI: Twenty seconds.

MS. PESCHIN: Lastly, the Alliance -- thank you. Lastly, the Alliance continues to call on our federal health agency leaders to be straight with policy makers and the public about what lies ahead in the COVID-19 fight without sugar coating or political spin. Please continue to champion science because science is what will save us. Thank you for the opportunity to speak.

DR. ATREYA: Thank you for your comments. The next speaker in line is Suzanne Robotti.

MS. ROBOTTI: Thank you. I'm Suzanne Robotti, the founder of MedShadow Foundation, an independent nonprofit health journalism site focusing on the side effects of medicine. We are very supportive of vaccination. In fact, one of our employees is a volunteer for one of the COVID-19 vaccination trials. We do not accept support from pharmaceutical companies or medical device manufacturers and therefore, I have no conflicts of interest. I have also served as a consumer representative on the FDA Drug Safety and Risk Management Committee.

An effective vaccine would save hundreds of thousands of lives and end the deeply damaging social separation we are suffering. But a faulty COVID-19 vaccine is more dangerous to population health than is COVID-19 itself. Rushing to market a vaccine with harmful and life-altering side effects would have decades-long repercussions. A flawed vaccine would

increase fear in the public of all vaccines. And hope of gaining the trust of those suspicious of vaccines would be lost.

COVID-19 is dangerous but not as dangerous as the recurrence of measles, whooping cough, mumps, polio, and more. The FDA has indicated that a vaccine need only prevent or decrease COVID-19 severity in 50 percent of the people it's given to. But 100 percent of the people given the vaccine will risk a side effect. The vaccine must be engineered so that those who get no benefits from the vaccination aren't also risking a lot of harm. A COVID-19 vaccine could be given to 300 million people in the U.S. alone. Even if side effects so rare as one out of every 10,000 patients would end up impacting 30,000 people and their families.

When testing a drug or a vaccine in a vulnerable population, there will be adverse events. And the only way to tell if an adverse event is the result of the vaccine or if it's a drug interaction or

are the result of underlying condition of the patient is if it is tested in tens of thousands of people for many months and years. Even after a vaccine is approved, you must ensure the post-approval testing is robust.

I am asking the committee to ensure that the path to vaccine use through approval or EUA or any other method protects the citizens that you represent. Do not trust pharmaceutical companies to get it right. We've been unhappily reminded most recently with pharma, that pharmaceutical companies may take shortcuts. As Dr. Cody Meissner was quoted and saying today, we're going to get one chance to introduce the vaccine. If that goes badly, it's going to be a long time before we get another COVID-19 vaccine.

MR. KAWCZYNSKI: Twenty-five.

MS. ROBOTTI: Thank you. I appreciate your work.

DR. ATREYA: Thank you for your comments. The next speaker is Dr. Dorit Reiss. I came to know that

she's not available at this time. Thank you. We'll move on the next speaker, Ms. Nissa Shaffi. Ms. Shaffi?

MS. SHAFFI: Yes, thank you. Can you hear me?

DR. ATREYA: Yes. Go ahead, please. Thank you.

MS. SHAFFI: Great. Thank you so much. Good afternoon. My name is Nissa Shaffi, and I'm here today on behalf of the National Consumers League. I have no relevant conflicts of interest regarding today's remarks. For over 120 years NCL has advocated on behalf of consumers who depend on vaccines as life-saving medical intervention. NCL has advocated on behalf of consumers who depend on vaccines as life-saving intervention. We extend our gratitude to the Vaccines and Related Biological Products Advisory Committee for all that you do to protect public health and for the opportunity to speak here today.

Today NCL would like to highlight the following priorities. The deployment of Emergency Use

Authorization, the safety and effectiveness of the vaccine, and inclusion of diversity in clinical trials. These three concerns align directly with NCL's efforts to enhance vaccine confidence and uptake, especially in the context of the pandemic.

We trust that the FDA will release the vaccine upon careful consideration of its safety and effectiveness. Post-market surveillance of the vaccine is imperative to determining the ongoing efficacy of the vaccine. Implementing the release of the vaccine on such a magnificent scale will involve precise coordination that traverses all levels of government. And consumers will rely on public health agencies to communicate and respond to any potential adverse events regarding the COVID-19 vaccine.

There has never been a more critical time for consumers to have confidence in the Food and Drug Administration. The FDA is entrusted with ensuring the safety, efficacy, and security of the treatments needed to treat and prevent the spread of the virus.

Throughout the pandemic consumers have received conflicting information from the administration on various COVID-19 treatments. We are aware that developing a vaccine for COVID-19 is a time-sensitive priority.

However, we are concerned that consumers may believe the FDA is hastily approving investigational tests and drugs. NCL appreciates the FDA and recognizes that EUA is not intended to replace randomized clinical trials and that clinical trials are clinically important for the definitive demonstration of safety and efficacy of a treatment. Through our education and outreach to consumers we support the FDA and its efforts to develop a safe, effective, and expedited pathway towards a COVID-19 vaccine.

Finally, to mitigate the disproportionate disease burden experienced by people of color during the pandemic, NCL requests that clinical trials for the COVID-19 vaccine are inclusive and consist of diverse subjects. People of color are significantly

underrepresented in clinical trials and undertreated in medical settings. This phenomenon will prove --

MR. KAWCZYNSKI: Twenty seconds.

MS. SHAFFI: -- thank you -- phenomenon will prove to be a challenge when encouraging vaccine uptake. Ensuring adequate representation in clinical trials will foster vaccine confidence across all demographics. In closing, to stem the tide of vaccine-preventable diseases, NCL submits these comments for review by the committee to ensure that consumers are afforded with safe and effective vaccines to combat the pandemic. Thank you for your consideration for our views on this important public health issue.

DR. ATREYA: Great. Thank you so much for your comments. The next speaker is Mr. Mitchell Warren.

MR. WARREN: Thank you very much. My name is Mitchell Warren. I'm the Executive Director of AVAC, a nonprofit organization that for 25 years has worked to accelerate the ethical development and global delivery

of HIV vaccines and other new prevention options. In March we joined with several other organizations to establish the COVID-19 Advocates Advisory Board, a global partnership to engage civil society to accelerate R&D and eventually delivery of COVID-19 vaccines. I have no conflicts to declare, and we accept no funding from pharmaceutical companies.

I want to acknowledge and support the FDA guidance documents on both the licensure and on Emergency Use Authorization from June and October. Both documents set important criteria that should be viewed at the absolute minimum requirements for FDA action. And that any action requires this committee's positive recommendation needs to be a director outcome of today's meeting.

I should say that while this committee and the FDA are, of course, focusing on the U.S. by statute, what happens today in this virtual room has global importance. No pressure, but what happens in the coming days, weeks, and months through this process and

your actions and deliberations will either enable or inhibit our collective ability to translate clinical trial results into public health impact and to instilling confidence in vaccines and regulatory processes generally.

As you deliberate today and in subsequent meetings with each application, we urge you to consider the following. One, of the critical importance of distinguishing between an EUA and a licensure under a BLA and ensuring that any EUA places specific requirements for continued data collection and clearly articulated pathways and timelines for a full BLA. If an EUA is granted, the committee and the FDA must make clear that the EUA is not in lieu of an approval, a signal that licensure is imminent or guaranteed, or promoted or described as pre-license.

Further, you must place strict requirements on the continued data collection in ongoing blind clinical trials that are going to be required for possible future BLA. An applicant should be required to present

a timeline for that submission.

Two, the need for inclusion of diverse populations in the trials and the accrual of relevant safety and efficacy data across those populations. If an EUA or BLA application does not provide adequate diversity across age and population, we urge the committee to determine strict requirements to place on the applicant. A partial authorization or approval will further diminish trust and confidence.

Three, the importance of broad community engagement and development and implementation of trials as well in the review of applications. Any COVID-19 vaccine that proves safe and effective will need to be introduced at scale and with speed never previously seen. The importance of community engagement cannot be underestimated, and we urge you and the FDA to support the inclusion of strong civil society voices and community perspectives as part of the regulatory process and the future committee meetings.

Fourth, clarifying the initial authorization

or licensure of one vaccine on the design and conduct of future trials. As the committee and the FDA --

MR. KAWCZYNSKI: Time.

MR. WARREN: -- review these applications, it should be critical to consider the implications of approving a product of only 50 percent efficacy, and we urge you to start now to develop clear --

MR. KAWCZYNSKI: Time.

MR. WARREN: -- additional FDA guidance documents to help with those discussions. Let me thank you for your work and your commitment to a science, evidence-based process to instill confidence throughout the way. Thank you.

DR. ATREYA: Great. Thank you so much, sir. Last speaker for today will be Ms. Kim Witczak.

MS. WITCZAK: Good afternoon.

DR. ATREYA: Okay.

MS. WITCZAK: Oh. Good afternoon. My name's Kim Witczak. And I'm calling in from a snow Minneapolis. I am speaking on behalf of Woody Matters,

a drug safety organization that started after the death of my husband due to an undisclosed side effect of an antidepressant. I have no financial conflicts of interest. I'm also on the board of directors for the USA Patient Network, an independent patient voice advocating for safe, effective, and accessible medical treatments. We make sure the everyday, real-world patient perspective is represented in healthcare conversations.

The discussion you're having today reminds me of the famous ad campaign for Rolling Stone magazine, perception versus reality, perception of a vaccine for disrupting severe COVID-19 versus the reality of what's actually being studied and evaluated. Through the help of media, government officials, and important public health organizations the perception is that vaccines are key to getting our lives back to normal. The perception is that this vaccine will help keep people from getting very sick and dying while preventing infection and disease transmission.

However, the reality is the trials were not designed to test whether the vaccine reduces the risk of severe COVID-19 or reduces the risk of hospitalization, ICU, or the spread of the virus. Nor does it include some of the -- including the most at risk like the elderly, immune compromised, and other comorbidities. According to the FDA guidance, just a 50 percent efficacy with an allowable margin of error as low as 30 percent is acceptable -- hardly a high bar to gain public trust. The reality is vaccines were designed with speed in mind.

Historically, vaccines have not been a quick solution as they can sometimes take decades to become effective. Like the virus itself, there are so many unknowns with the vaccine that need to be figured out like does it need to be taken in multiple doses, will it need to be tweaked and given every year like the flu shot? These are things we still don't know. And we haven't even begun to scratch the surface of the potential short- and long-term safety issues with these

new vaccines and the adjuvants that are being used.

Transparency is crucial. We need to shoot straight with the American people. We deserve to have an ongoing, open, civil debate of the merits of the changing science, protocols, the evidence, and the harm in real time. Ideally, these vaccines would be reviewed by independent scientists and researchers without any ties to vaccine makers or have any financial or political agendas motivating decisions. A lot is riding on COVID --

MR. KAWCZYNSKI: Fifteen.

MS. WITCZAK: A lot is riding on COVID vaccine approvals not to mention the billions of dollars being spent from governments around the world. The public wants more than just some vaccines out in hopes that something sticks. It is the American public that will ultimately pay the price, all while the companies manufacturing vaccines have been given complete legal immunity should something go wrong.

Speed isn't everything. I believe there is

still an opportunity to course correct and make changes so that we don't end up with an approved vaccine that reduces mild cases in health people but does little to protect the most vulnerable --

MR. KAWCZYNSKI: Time.

MS. WITCZAK: -- and plays up the perception of having effective and safe vaccine to stop COVID-19. We need to stop, pivot, and do the hard right, not the quick, easy wrong. Thank you, and I know and I appreciate all the hard work you're doing because I'm currently a consumer representative on another FDA committee. Thank you.

MR. KAWCZYNSKI: Thank you.

DR. ATREYA: Great. Thank you so much Ms. Witczak. This concludes the open public hearing session for the Advisory Committee Meeting today. Thank you all. Bye bye.

COMMITTEE DISCUSSION AND RECOMMENDATIONS

MR. KAWCZYNSKI: All right. Okay. Dr. Monto. There you are, sir. Let's make sure we got your audio back. There you go.

DR. MONTO: We are about to launch into a two-hour distribution of the questions that the FDA has asked us to consider. So if we could see those questions? And the first are really related because we are being asked to look at the FDA's approach to safety and effectiveness in the guidance documents, which include guidance for both EUA and pro-licensure, and then to comment about, in question number 2, how if EUAs are granted, how there would be continued blinding in the clinical trials. The first question is also --

DR. GRUBER: Dr. Monto.

DR. MONTO: Yes.

DR. GRUBER: Dr. Monto, can I make a couple of comments?

DR. MONTO: Would you, please?

DR. GRUBER: Okay. Thank you so much. So first of all, thank you for introducing these

questions. And I thought while the third discussion item may be rather self-explanatory, maybe the first two discussion items require some clarification. And I wanted to make a couple of comments regarding each of them.

So discussion item 1, that you just read, that we would like for you to discuss FDA's approach to safety and effectiveness data is outlined in the respective guidance documents. Now we do realize that these guidance documents are long and comprehensive, and they have a lot of information in them. So what we would like for the committee to really focus on is we would like to hear are we on balance? Did we strike the right balance? On one side, we want a safe and effective vaccine available to the public as soon as possible, but on the other side we do realize that this cannot come at the cost of public health.

So what we would like for you to opine on is specifically are there areas or recommendations or data needs that are discussed in these guidance documents

that you think as a committee are too strict or conversely are they not strict enough? Are there areas of broad disagreement in some of these guidance documents or is there broad agreement? So this is what we would like for you to discuss rather than really going into each detail of the data needs discussed in this guidance document.

Now question 2 -- and I would like to pause on this a little bit and give a bit more background. So we discussed -- we asked the committee to discuss the consideration for continuation of the line that Phase 3 clinical trials in the event that an EUA has been issued. And Dr. Weir and Dr. Fink this afternoon explained to the committee that for a preventive vaccine that is intended for use under an EUA in potentially millions of people, the data that the FDA would request to support the benefit of the vaccine should be very close to meeting the standards that would support licensure.

And Dr. Fink also explained why an issuance of

an EUA should not in and of itself require unblinding of a COVID-19 vaccine. And we are concerned about the risk that use of a vaccine under an EUA would interfere with long-term assessment of safety and efficacy in ongoing trials and potentially even jeopardize product approval in not only the first vaccine but maybe even follow-on vaccines.

And continued follow up of clinical trial participants to further refine efficacy estimates to look at durational protection and the potential for enhanced disease and to obtain the required safety follow up is essential and can't really only be successfully accomplished ideally with keeping these trials blinded. And that's why we're asking you to discuss this question if there are other considerations.

Now in the interest of transparency, and Dr. Kurilla brought this up this morning, he asked about why the agency has not contemplated expanded access. And Dr. Fink summarized this very elegantly and also

pointed out that there are some -- there are complexities for a national expanded access program.

But in the interest of transparency and to explain to the committee that we have an additional provision to make investigational products available, I'd like to show five slides real quickly to explain to you our expanded access regulations and, again, just for the purpose of transparency and put that on the table.

So as Dr. Fink explained earlier on, the expanded access regulations are really to facilitate availability of investigational drugs to patients with serious or life-threatening diseases or conditions when there are no satisfactory alternatives. And the primary purpose of an expanded access program is to treat the patient's disease or condition. Can I have the next slide?

Okay. So we have three categories of expanded access, and I'll be discussing only the treatment IND or treatment protocol because that really calls for

widespread treatment use of a product. Next slide, please. So there are requirements for all expanded access uses. First of all, the disease must be serious or life threatening, and there is no satisfactory alternatives. Again, the potential benefit needs to justify the potential risk of the treatment. Hence, providing the investigational drug will not interfere with clinical development of the product for that specific use. Next slide. Next slide, please.

Now there are three categories, as I mentioned, and within each category there are additional criteria that must be met. We want to skip this slide and the next slide and go straight to, I think, slide number 6. Six, please, slide number 6. Can I have slide number 6? Thank you.

So under expanded access use of a treatment protocol, and that really means widespread use, the FDA must determine that the drug is being investigated in a controlled clinical trial under an IND that is designed to support marketing application. So that is the Phase

3 clinical trials that are currently ongoing to use the example for COVID-19.

The sponsor has to pursue marketing approval. And for a serious disease such as COVID-19 we need sufficient clinical evidence of safety and effectiveness to support expanded access use ordinarily from Phase 3 trials but could also come from compelling data from Phase 2 trials. Hence, we need available evidence that provides a reasonable basis to conclude that the investigational drug may be effective and would not expose patients to unreasonable and significant risk. And such evidence also could come from Phase 3 and 2 trials. And the last slide, please? Slide number 7.

As Dr. Fink explained, we would require expanded access submission. And this can be a new investigation, new drug application, or an amendment to an existing investigation and new drug application. These are clinical studies that are conducted under informed consent and IRB approval. There is a

requirement for safety data that is adverse event reporting. And we need accurate case histories and drug disposition records. And there are other investigative responsibilities that may apply, depending on the type of expanded access.

So that concludes that slide presentation. I just wanted to inform the committee of this additional provision to make investigational products available. Thank you.

DR. MONTO: Hello, Dr. Gruber. Is the expanded use authorization usually done for drugs or for vaccines?

DR. GRUBER: The extended access regulations and provisions do apply to biologics and to vaccines and we have been using these extended access provisions for vaccines lately. Not under treatment IND, under widespread use. But they have been used a couple of years ago when we had the Meningococcal Type B outbreak at universities. And it's also being used to make yellow fever vaccine available in the United States.

So we have been using those for vaccines. But again, treatment IND means widespread use.

DR. MONTO: Thank you.

DR. GRUBER: Mm-hmm.

DR. MONTO: Okay. So let's go back to our discussion of item number one. And I did cut off the questions that were being given to Dr. Fink and Dr. Weir. And if we still have questions about EUAs and BLAs they are available for us right now. So raise your hands if you do have continued questions. Okay. Mr. Toubman.

MR. TOUBMAN: Yes. Thanks. So I did have questions and it turns out that the public speakers during the open hearing sort of emphasized some of these points. I'm glad that I didn't get to ask them beforehand. Two questions related for Dr. Fink specifically. Two related to either licensure or EUA, and one specifically to EUA.

The endpoints I myself in reading the documents, and again I'm a layperson so bear with me.

But I was concerned that the endpoints did not require serious disease, even moderate to serious disease, only some symptomatology. And the concern there is that we could have a vaccine that seems to do well meets the 50 percent test, and it's effective in avoiding mild cases but actually does very little to address what we really care about, which is serious disease and deaths.

And the way it was described in the documents is that it's a choice whether to use that as a primary endpoint but if not, it should be a secondary endpoint. And as I understand that, contrary to one of the speakers only -- there is one company that is -- one sponsor that is using it as a primary endpoint, moderate to severe disease, but only one. And the other it's the secondary endpoint.

And my understanding, correct me if I'm wrong, my understanding is that that really is significant because the 50 percent efficacy test is only being applied to the primary endpoint. So it may not actually do well with the primary endpoint of avoiding

any kind of disease at all but do very little, and it'll still pass the test. So my question is, why would that not require the primary endpoint is serious disease?

The second question and this is because there's different information here, we read about the 50 percent and it was repeated again today. But this morning, Dr. Martson from NIH said -- and, you know, Dr. Monto followed up on that, that 60 percent. And I certainly could see the argument for 60 percent in the situation where we also have problems of uptake, maybe 60 percent is warranted. But my question was, why the difference between the 50 and 60? Why is it not 60?

And then my last question related to EUA is, this came up in the public hearing as well, two months. A median of two months to experience post -- the final regiment, the second dose if there's a second dose. And it was pointed out that means half the cases won't have been -- people won't have been inoculated for two months, that it'll be less than two months. And the

explanation we were told that the document says that most of the adverse effects occur in the first six weeks. But they could be longer than that and we're talking about drugs based on untested, or I should say unused platforms that have never been the basis for vaccines.

So there could be adverse effects we don't know about. And so isn't two months a little short? And in finishing this question I would note that the WHO has a three-month minimum test for their, what they call emergency use lifting. I don't know how different that is from EUA, but it does seem that one very respected official body is looking at this whole problem as it should be at least three months. So if you could answer those three questions, I would greatly appreciate it. Thank you.

DR. FINK: Hi. Thank you for those three questions. I'll try to answer them in order. So the first question was about the primary efficacy endpoint being any disease versus being severe disease. You

know, here we are really trying to strike a balance between getting information on the most clinically significant outcomes of COVID-19 and how a vaccine might be able to prevent those outcomes, versus being able to make an impact on the pandemic in as reasonable amount of time as possible based on good data.

And so, in trying to strike this balance and also really having to acknowledge that the vaccine manufacturers are free to choose what they consider to be the most relevant primary endpoints for their vaccines. And then we evaluate whether the data supports that the vaccines are effective for that specific indication. And then other bodies, such as ACIP determine whether the vaccine should be used in certain situations. We felt that we could not mandate a specific primary endpoint, including a primary endpoint that focused on severe disease.

Now, that being said, when we do make our benefit/risk determination for NEUA or for licensure we do expect to have data to inform whether the vaccine

is, or may be, effective against more severe disease. We -- because more severe disease is going to be less common, then we will unlikely have in an analysis that used a less severe disease endpoint as the primary analysis. We will unlikely have, with the same degree of statistical rigor, evidence to determine effectiveness against more severe endpoints. But we do expect to have some, and we will use that evidence as one piece of information to inform our benefit/risk determination.

I'll also mention that there are multiple examples of vaccines where the data do appear that the vaccines are most effective against more severe disease, less so against less severe disease, and even less so against asymptomatic infection. So we took that experience into consideration as well.

To answer your second question about 50 percent versus 60 percent, I'd have to go back to Dr. Marshton's slides to remind myself of whether 60 percent was a success criterion that had been outlined

for specific study or an assumption of vaccine efficacy that was used to calculate a sample size for that study. I think it might have been the latter. We, as I mentioned before, we make our recommendations based on what we think is an efficacy standard that would be needed to make an impact on the pandemic. And of course, we would not argue with any study that aims to go higher.

Lastly, in terms of the two-month follow-up, we do recognize that other organizations and individuals including WHO have specified and advocated for a longer follow-up duration. Again, this was a consideration of balance in terms of having the amount of safety data that we thought was absolutely necessary to inform a benefit/risk consideration given what we know about vaccines and vaccine safety in general, and the goal of actually not withholding a vaccine that could make an impact. With the trials that are currently underway, we do acknowledge that some subjects will have been enrolled later.

Some subjects will not have quite two months of follow-up at the time an interim analysis to supporting the EUA might be conducted. But we are still talking about many thousands of vaccine recipients for which two months or more of safety and efficacy follow-up data would be expected to be available. Thank you.

MR. TOUBMAN: Thank you. I'll have comments about that, but I appreciate the answer. Thanks.

DR. MONTO: Yes. Dr. Kurilla.

DR. KURILLA: Thank you. Yeah. Doran, I figure if I don't ask the question here, I'm never going to get an answer. There's been a lot -- well, not a lot. But there's been some scientific discussion of non-coronavirus vaccines, BCG, OPV, MMR, having a potential role in reducing severity of COVID disease. As far as I'm aware there are some trials that are going on. So I guess one question, which you probably wouldn't share is whether you've been approached by investigators?

But I'm wondering how the FDA would handle that. Would you treat them by the same criteria for coronavirus? The real -- not a concern, but the potential outcome is a positive readout of a clinical trial may because these are commercially available, licensed vaccines, we may actually end -- we could end up in a case of vaccine shortages for some of these other vaccines if they were to be positive. I'm just wondering what the -- how the FDA would handle those.

DR. FINK: Right. So the best that I could say is that our EUA guidance and our June guidance don't specify what the vaccine components need to be. And of course, as you mentioned, I can't divulge any information about studies that might be underway under IND. You know, really, this VRBPAC is intended to focus on those vaccines that are, you know, in Phase 3 trials currently for which we might expect to have data soon. And so I really would like the discussion to focus on those vaccines. And I'll invite my colleagues at CBER to add anything if they have anything to add.

DR. MONTO: I think your answer is pretty specific about what our scope of interest is right now. We're not going to be looking at other interventions. We have a very long list of those who want answer -- I'll get you to answer some questions right now. I want the committee to know that we are going to have a general discussion and I want to restrict the questioning right now to those people who want to get further information about EUAs and BLAs and the rest, because we need to move on to the more general discussion. So please, if you don't need a specific answer just please lower your hands and then we'll recognize you when we get to the more general discussion. So, Dr. Pergam.

DR. PERGAM: Thanks. One of the questions I had was related to the -- an EUA. It said 50 percent of the patients will be followed with at least two months of efficacy and safety, and then you also mentioned that it's 3,000 older patients must be included in that UA. My question is, I know that

enrollment has been difficult in high-risk groups, particularly the racial minorities.

And there's no specification about including the appropriate number in the EUA specifically that I could find that suggest that it would be equal numbers based on what the trials should look like. And I'm concerned that if an EUA's put forward without adequate enrollment in those particular racial minorities that, that might be seen in a negative light. So I'm curious how that was decided and is there any thought about modifying that specifically?

DR. FINK: Can I just ask for a clarification? What are you asking -- how is what decided?

DR. PERGAM: Yeah. So I'm saying for the time point where the EUA -- you said you wanted at least 50 percent of the population that's had both efficacy and safety data of two months, but there's no pre-specification about racial breakdown in that group. Does that make sense?

DR. FINK: Yes.

DR. PERGAM: Yeah.

DR. FINK: Right. So, you know, we have not ever had requirements for demographic composition of data to support licensure of a vaccine and I think it would be very difficult to outline such requirements for EUA. Now, that being said I think we all understand, and agree with, and support the importance of having a diverse study population that is able to provide safety and effectiveness data across the demographic spectrum. That is the goal.

And so one way in which our regulatory action can help to ensure that the vaccines being deployed are safe and effective for the entire population for which it is authorized is to make sure that the entire population for which it is authorized actually has data that supports the safety and effectiveness. So we will be looking very closely at an EUA application to see where the gaps are in terms of demographic representation.

DR. PERGAM: Thank you.

DR. FINK: But I also have to caution that, you know, we have had situations where, unfortunately, you know, licensure applications have come in with less than desirable representation in certain, you know, say, racial or ethnic groups. That wouldn't a priori be a reason to restrict the vaccine from use in those groups. I just want to make that clear.

DR. MONTO: Dr. Nelson.

DR. NELSON: Can you hear me now?

DR. MONTO: Yes, we can.

DR. NELSON: Fantastic. Well, thank you. Well, thank you again for your patience with us as a committee and hopefully with this quite related question as well. So in our current state when the entire world is indeed looking for the vaccine, who specifically wants an EUA would be authorized, have access to that vaccine? I say this in reference to your last bullet on slide 13 which states, as with vaccine licensure an EUA would specify use in those populations for which available data supports favorable

or benefit/risk.

So just like the last questioner asked, we're all anticipating that the initial application for EUA will have insufficient enrollment for some of these higher-risk groups or underrepresented groups. Does that mean when the EUA's authorized if there's not enough data for those groups they will be excluded from having access to that vaccine under the EUA? And your particular thoughts on the heels of Dr. Offit's question this morning about the potential for offering an EUA and extending the time to which applicants will really bring their vaccine for full licensure?

DR. FINK: Right. So to answer the first question first, we -- as I mentioned in response to the previous question, we will look carefully at the demographic representation for safety and effectiveness data, and we'll approve or authorize the vaccine for those populations for which the data support safety and effectiveness and favorable benefit/risk. There may be circumstances in which demographic representation is

less than we would like, or not large enough to make firm conclusions. But those types of gaps would not necessarily in and of themselves result in a restriction.

We would have to think about whether it makes sense from a scientific basis to be concerned that there is some difference based on differences in demography to result in such a restriction. The most common example that I can think of would be age. We do not automatically assume that if the vaccine works for one age group that it will necessarily work for another.

And so, for example, if we had very limited data on safety or effectiveness in elderly individuals, that would cause us concern and we would have to consider whether the data really did support authorization or licensure of the vaccine for use in an elderly population. And could you repeat your second question?

DR. NELSON: I think the second question was,

with the potential for delays in bringing vaccines for full licensure, some of the excluded groups who aren't part of the initial EUA might have to wait even longer. And I think if you look at what some of the strategies for deployment, there may be disconnects between the initial intent of deploying the critical infrastructure individuals and higher risk patients where we may not have the sufficient benefit of data for both safety and efficacy. So you see the dilemma that has been presented and outlined by our public testimony earlier today, that there is great concern about being able to acquire that data in these specific settings. Thank you.

DR. FINK: No, I couldn't agree with you more. We fret about that constantly. And so that --

DR. MONTO: Dr. Gans. And then, we've got a couple more, and then we'll get you off the hook right now.

DR. ALTMAN-GANS: Can you hear me? Hi. Thanks so much for entertaining our questions. Mine is

quick because I can save some of mine for the discussion. But I really wanted to know and I haven't really heard much, I mean, we know that a lot of people have questioned the efficacy point of the 50 percent meeting cases.

And I haven't heard how that's being impacted by all our other public health strategies, and what if we actually don't see with people's behavior these kinds of numbers that we need to even establish that timepoint. I worry a little bit about that. And that's my first question just for thinking about the epidemiology of this and hitting timepoints even though those are even low for some people.

The other thing is, in all of your safety data I really don't see how the uniqueness of this virus and some of the components of its immune responses, not so much for immunogenicity of a vaccine but for safety reasons in terms of the immune and thrombotic events. I see none of that in, sort of, the FDA thinking in terms of vaccine safety, which actually may be markers

before the clinical disease. And waiting for those clinically is maybe something we can't afford to do with this particular virus.

DR. FINK: All right. So what you're describing, these concerns that are, you know, they're theoretical but they're certainly well-founded theoretical concerns, we are interested in them. We mentioned enhanced respiratory disease in our guidance as an example of a type of immune-mediated process chiefly because it's been described with another respiratory virus vaccine, RSV in the 1960s, and there were some animal data with SARS-1 vaccine candidates that raised that concern.

So I don't want the committee to come away with the impression that we're thinking of enhanced respiratory disease as the end-all-be-all of these types of concerns. We are concerned about phenomena that might manifest similar to MIS and other immune-mediated processes. And of course, we will be examining adverse event data that comes in with the

safety follow up looking specifically at events that might be signals for these types of phenomena.

DR. MONTO: Dr. Fink, have you thought about changing the guidance to enhanced disease instead of enhanced respiratory disease?

DR. FINK: Sorry, my lights just flashed off. That is certainly food for thought. But I do want to make clear that we are thinking about it.

DR. MONTO: Okay. Dr. Hildreth. Long list here.

MR. KAWCZYNSKI: Dr. Hildreth, you have your own phone muted. Go ahead. See if we can hear you now. Dr. Hildreth, we're still -- you still have your own phone muted, sir. Sorry. We're going to go to the next one, Kathryn Holmes, while you get your audio unmuted, Dr. Hildreth because we can't hear you. Kathleen Holmes.

DR. HOLMES: I wanted to raise a -- can you hear me okay?

MR. KAWCZYNSKI: Yes, we can.

DR. MONTO: We can hear you clear.

DR. HOLMES: I wanted to raise a different question. Based on what you recently said it seems to me that this is a giant experiment that's being done with many vaccines and will be possibly having a great deal of data which can inform a lot of information about this disease and this virus. We anticipate having future COVID-like diseases coming about and we need to find out as much as we can about these various platforms as soon as we can. But one of the things that I have not heard much about during this conversation is infection.

I'd like to see how we could actually be measuring infection rather than just mild disease. And rather than saying what we should be trying to do is developing a vaccine for the most seriously affected people, we should be looking to see what can prevent infection because that is the rubric which would prevent spread through the community most effectively. And that is what will protect our elderly as well.

And so there is a new assay for detecting antibody in the saliva. And I think if people used that as a test periodically after vaccination to see if people had been infected sometime, you know, use at certain intervals it would not be onerous for the vaccinees to be assayed in that way and they could pick up which people had been infected. You made the assumption that mild cases and inapparent cases had less immunity, but that may not be true for this virus. We don't know.

But all that data is out there and accessible in the populations that are being tested now, and we should be collecting that kind of data. And I don't know whose responsibility it is to do that during this time, but it seems a terrible thing to let that kind of data go to waste when so much money has been poured into this. And one of the questions that's very important to ask is, can you prevent infection as well as a treatment for the disease?

DR. FINK: Yeah. I couldn't agree with you

more. That is a very important measure to evaluate and of course sterilizing immunity is the gold standard of protection but of course not always achievable. In our June 2020 guidance, we did make a recommendation that prevention of infection should be evaluated, if not as a primary endpoint then as a secondary endpoint.

And that endpoint could be evaluated using either serologic methods similar to what you described. Not necessarily in the saliva, but that would be an option, or through periodic sampling using virologic methods. Although, those would have to be frequent enough so as not to miss cases due to only transient shedding. So we do agree with you that evaluation of prevention of infection is important, we have recommended that studies do that.

DR. HOLMES: But I don't think that it would be very practical to do that with serology to get a lot of volunteers to take a lot of blood tests over time. Whereas the saliva test which was just recently validated I believe would perhaps be more accessible.

And it would be wonderful if -- I don't know if the companies would do this, but if data like that could be made accessible to investigators who would be able to use that data. And I don't know how that kind of information is shared in order to learn that amount of information about the virus itself.

DR. FINK: Thank you.

DR. MONTO: Okay. David Wentworth?

MR. KAWCZYNSKI: Did you want to give it a chance again?

DR. WENTWORTH: Sure. I'll try to be brief. Thanks very much for staying on with us, Dr. Fink. I had a question related to this two-month pre-market follow up again. So I think, you know, some of your rationale, some of the rationale presented is quite strong. But here we're dealing with some, you know, generic recommendation and some very new platforms, such as mRNA as a platform. And that's very different than most of the things that have been given to people at large, in large amounts, being mostly either just

for combat proteins or purified proteins from viruses, et cetera.

And so I guess I wonder, did you consider a longer time frame depending on, you know, the platform itself? Here you're talking about a spike glycoprotein that interacts with a receptor that has physiologic, you know, responses that it controls, and you don't exactly know where all these lipid nanoparticles are going to end up in the host. So I guess I was just wondering, is there any idea to do a longer pre-market follow up for those, kind of, more unique platforms that we have less of an understanding of?

DR. FINK: Right. So first of all just to clarify, when you talk about pre-market follow up, we're really talking about six months. The two-month benchmark is to support EUA, which, you know, is a somewhat different benefit/risk calculation although not that different when you're talking about millions of people, admittedly. So, you know, we regulate vaccines of all different technologies as Dr. Gruber

explained in her introductory comments. We have the same set of regulations that apply to all vaccines independent of what the platform technology is.

Again, we did consider novelty of platform among all of the variables in our considerations but ultimately came out with our guidance as a way to strike a balance. If the committee has strong feelings or recommendations about how these considerations should be handled differently, then we would certainly want to hear that.

DR. WENTWORTH: Thank you very much.

DR. MONTO: Dr. Hildreth. Dr. Hildreth, are you there?

DR. HILDRETH SR: Yes, I'm here.

DR. MONTO: I don't think --

DR. HILDRETH SR: Yes, I'm here.

DR. MONTO: Okay. Now please ask your question.

DR. HILDRETH SR: Thank you, Dr. Monto. I just want to make two quick points with Dr. Fink if I

may. The first is that since severe disease and -- that occur primarily among minorities with this virus, if we put a vaccine out there that does not address that issue it's just going to perpetuate the perception that this -- that that population or that segment of our population does not matter much in dealing with this challenge. So I would just ask for consideration be given to making sure that whatever we do we have a vaccine that does address severe disease.

And I'd like to make -- the other point that you said you cannot mandate what the drug companies might set as their primary endpoints, if I'm not mistaken the taxpayers of the United States of America are paying a -- the tab for this, so maybe you might have more authority to mandate than you might think. I'm just -- want to put that out there. So I just want to make that point. Thank you.

DR. FINK: Thank you.

DR. MONTO: Thank you, Dr. Fink, for putting up with us for this long. I want to move the committee

to the discussion items now. And the -- I want you to think about our conclusions because we are being asked to summarize our conclusions and I think we can lump together one and two and come up with a single set of conclusions for both. But let's look at number one first. Please discuss FDA's approach to safety and effectiveness data as outlined in the guidance documents, which means both EUA and full licensure. I see Dr. Meissner has his hand up.

MR. KAWCZYNSKI: Dr. Meissner, you can turn your camera on, and I'll unmute you.

DR. MEISSNER: I just wanted -- I don't know if Dr. Fink is still on the line but I just wanted to clarify a point that I don't think is fully understood and that is that the FDA licenses a vaccine based on the data that are presented to the FDA. The FDA does not make recommendations as to how the vaccine should be used. That is the responsibility of the ACIP, not -- I don't know if Amanda's -- Amanda Cohn is still here but she might want to comment. But --

DR. MONTO: I can comment. You're absolutely right.

DR. MEISSNER: Okay. Thank you. I -- but I think it's important for people to understand that.

DR. FINK: Yeah. Thank you very much for pointing that out. I tried to touch on that when I was responding to one of the questions, I think, about demographic representation and what an -- what population an authorized use might include. And, of course, I think it's helpful to clarify that FDA does not have the authority to mandate demographic representation in clinical trials. We're required to report to Congress about demographic representation in clinical trials that support licensure of a product, but we can't mandate that.

What we can do is make sure that the product labeling accurately reflects the available data so that recommending bodies such as ACIP, and also individual healthcare providers, and patients, are able to see whether the data applies to them and to make decisions,

whether it's for use in individual or use in a large population, about whether the data would support that use.

DR. MEISSNER: Thank you.

DR. MONTO: Thank you. And you can -- we can -- you can only review and make decisions about what is presented to you and that's why we really need to have a discussion about the guidance documents because that's what we have to go on. And we're being asked to look at them and to see if we agree with the approaches in the guidance document, and what we think about them in terms of their implementation. So let's get back to the guidance documents and Dr. Notarangelo, you have your hand raised.

DR. NOTARANGELO: Thank you. So I would like to echo what others have already mentioned. And I am specifically now looking at the document. I have problems with the standardization of efficacy. I -- first of all, I do appreciate that it's very important to standardize efficacy across multiple trials,

multiple platforms. But the problem is that these efficacy measures that are included in the document, they have two problems. First of all, they really are biased (inaudible) with mild disease. And that is a concern that I do share with Dr. Holmes actually. Her consideration that much more emphasis should have been put on actual infection and perhaps on severe disease at the same time. Mild disease may not mean very much.

The other problem with those efficacy measures is that most of them are really subjective. There are very, very few that can be actually objective measures. And I think that's a major concern. I mean, we're relying basically upon reporting from the subjects without any objective validation of what they're reporting. I'm really concerned about this. And this applies to the EUA and to licensure, in my mind.

A few other comments, I agree completely with Dr. Meissner. I think at this point based on what we've been presented I am very concerned about extending the, you know, immuno-bridging from adults to

children. I think children at this point should not be considered for use of this vaccine until there is sufficient evidence, and what we've been presented today does not provide that.

And finally, I think given that we are dealing with new platforms, I don't really understand the reason why the manufacturing facilities are not inspected. I think that is something that could be done. It could be done even ahead of time. I think it would provide some additional, you know, trust into the process.

Finally, you know I understand that we, you know, the FDA cannot mandate demographic breakdown. But I do agree with Dr. Hildreth that if we do not have sufficient evidence that the minorities, and in particular our black population are included in this, you know, trial data, their trust will diminish even farther.

And the net effect will be that perhaps the white population might be protected and we will only

see cases of severe COVID among the black, which would be a total disaster from a, you know, social standpoint. So I don't know what can be done but something should be done to facilitate the inclusion of a vulnerable population, in particular the black population in -- at this point. Thank you.

DR. MONTO: Dr. Chatterjee.

DR. CHATTERJEE: Yes. Thank you. You know, as I have been listening to the discussion and the presentations today, this thought has occurred to me over and over again, that what we're being asked to do is to build this plane as we fly it. And, you know, in the face of a pandemic that is killing hundreds of thousands of people across the globe, while we would like to see some of the data and the rigor in the scientific rigor in the studies, I do think that we have to weigh those two things as we deliberate on what data are needed to ensure, first of all, safety.

I think from the public hearing comments as well as the comments that were provided by the Reagan-

Udall Foundation folks, it's very clear that the public has significant concerns about safety. And so I think, for me at least, the most important thing is to make sure that whatever products are put on the market under whatever mechanism, whether it's a BLA or an EUA, that first and foremost these are safe. And then you get to the effectiveness piece of it which I think is also critically important, not less so necessarily, but I prioritize those two things, in my mind anyway, in that fashion.

And so the last thing I will say is with regard to the vulnerable populations around which there has been a fair amount of discussion as well, I do believe that it is again critically important, whether the agency has the ability to mandate it or not, it definitely has the ability to encourage the manufacturers and ask them to include these populations that are at the highest risk of poor outcomes from this infection. So as we consider what's going to happen with these products, I think it would be very important

for us to keep that last piece in mind. Thank you.

DR. MONTO: Thank you. Dr. Gans.

DR. ALTMAN-GANS: Thank you. I'm not going to reiterate things that have already been said about the efficacy and certain study populations of all which I agree with. My points are that in terms of number one I really feel like they haven't gone far enough in terms of the safety outlines, as people have indicated efficacy, as well. We really need to be thinking about this differently and we really need to be guiding what we do in terms of our safety. And some of the points I've brought up which I didn't feel like were fully answered in terms of some of the ways in which we know that it affects people and they're missing this in their safety data.

So nobody's collecting, as far as I can tell, anything about immunogenicity data and they're waiting for people to get clinical outcomes that would bring them to presentation. We have no immune markers, not thrombotic markers, which again, may actually be

biomarkers that precede some of this and could prevent people from having to become ill before we actually see an adverse event from a biologic. So that is a safety outcome that I think should be part of this.

The other part of this in terms of one, and we've already heard, which is around the EUA and the timeframe. And I think the public, as has been suggested, is probably not going to have an appetite for anything short of a vigorous process which we're used to seeing, is that we really have to have again differing approaches to the way in which we use our databases. It's not enough to do this kind of passive reporting that we have.

This is not going to be enough for this particular vaccine and the way in which we see the scrutiny. We don't have the time, we can't wait, and so we're really not utilizing our electronic capabilities at this point. This is going to feed into number three as well. And so I think that it's a really hugely missed opportunity that we're not going

to be able to turn around and do.

And only last point I will bring up is that some of these vaccine platforms may be more effective in certain populations. And unless we have an adaptive way of looking at those and looking across we don't want to bring -- we should have the ability to look at these vaccines in a more real-time fashion in terms of what we approve for what population. If one is better in the elderly versus some of our under-represented individuals, we should have that ability and we're not situated to do that. And this needs to be done. We need to look at these differently than we have looked at other vaccines since so many are being brought to the market. And the only --

DR. MONTO: Dr. Kurilla.

DR. ALTMAN-GANS: -- last thing I did want to say -- I'm sorry. The only last thing I did want to say is I think we shouldn't disclude the immune-bridging for children. I understand that there's real concerns about different safety issues. We should

absolutely have those involved, but, you know, that is something that has been done for other vaccines and it isn't something that we should completely, I feel, take off the table.

DR. MONTO: Dr. Kurilla. And please try to make your points on question one.

DR. KURILLA: Yes. Yes. So, yeah. With regard to the 50 percent efficacy, I -- to me that's a minimum threshold. But I think the issue here is that it's not a threshold for -- it shouldn't be the minimum for everything. And so I have some concerns about the utility of a 50 percent reduction in symptomatic disease when we don't really have any evidence that these vaccines are going to induce sterilizing immunity.

And so the idea for healthcare workers and other high-risk individuals, long term care facility staff, that sort of thing, something that would reduce their risk of infection -- that would take them nearly from a mild infection to potentially an asymptomatic

infection where they still might be infectious doesn't seem like it's something worthy of an EUA. Now, on the other hand, a 50 percent reduction in the progression in high-risk groups to serious disease, you know, that is actually very -- quite significant.

And so that is something that to me would be EUA-able. So, you know, for the first responders and primary healthcare workers and LTCF staff, the minimum has to be much, much higher in terms of having a general overall public health impact. And so, you know, I think -- it can't just be whatever group hits the target that's what gets EUA'd.

DR. MONTO: Dr. Kurilla, how do you do that from a feasibility standpoint? Having flexible outcomes for different -- flexible efficacy for different outcomes?

DR. KURILLA: Well, no. No. No. I did -- so they have their protocol, they have their trial design but when they do the -- it's going to be these interim readouts and you're going to get some assessment of

efficacy. Now, if they come out and say that, you know, normal, healthy adults we only saw 55 percent reduction in COVID, I -- that just doesn't strike me as something that I would want to EUA because I don't think it's going to have that significant of a public health impact.

Coupled with the fact that people get the vaccine and that they may in fact be unaware -- so almost half the people would be not protected. They may not -- and they may still get mild or asymptomatic disease anyway regardless of whether they've been vaccinated or not, no idea, unaware of their infectious state. Now, a 50 percent reduction in a high-risk group that goes on to more serious disease, that, I think is something that is -- that merits at least some consideration for an EUA. It would target those groups that are at a much higher risk.

DR. MONTO: Dr. Krause.

DR. KRAUSE: Yeah. Thanks, Dr. Monto. I just wanted to make a comment because it's very difficult

when thinking about different possible endpoints to think about what they mean. And of course, this also has to be thought about in terms of the frequency of each of these possible endpoints. So if the endpoint of the trials is severe disease, the trials may need to be almost ten times as big. And those trials would be infeasible, and we would never get a vaccine.

If the endpoints are infection, that can, with some additional work, be a feasible endpoint. But the science is not there to do that right now. So what we have looked at is the fact that a vaccine that is, in general, effective against mild disease, there is -- simply does not exist an example in vaccinology of vaccines that are effective against mild disease that are not more effective against severe disease. And so a 50 percent effective vaccine against mild disease is very likely to be greater than 50 percent effective against severe disease. And --

DR. KURILLA: Except Phil, many of the groups at risk for severe disease don't respond well to

vaccines in the first place.

DR. KRAUSE: I'm not hearing you, Mike.

DR. MONTO: Now, a lot of people want to make comments. Please.

DR. KRAUSE: And so that is the rationale. Now, the 30 percent lower bound is critical as well. And if you want to have a 30 percent lower bound for severe disease, that also makes the trial much, much bigger. But the trouble is, is that when you're dealing with many different vaccines, if you don't have stringent statistical criteria for success there's a very high risk that a vaccine that has marginal benefit, or possibly even no benefit, will meet the criteria just by chance. Because we're not talking about just evaluating a single vaccine, we're talking about evaluating multiple vaccines.

So if you're going to do evaluations of vaccines you have to look at what is feasible and what will give you the information that you need. And don't forget that these trials are intended to continue well

beyond whatever the timing of these interim analyses would be and will continue to gather information about impact on severe disease. And so they're designed to ultimately get the information that is needed.

And so one of the questions that you are being asked, of course, as a committee member, is what is the level that makes you comfortable with an EUA, or what is the level that makes you comfortable with broader deployment of a vaccine? And so that is, of course, a balance between looking at people's rights to take something where it's determined that the benefit might exceed the risk, while also making sure that we don't interfere with the public health good, the public good associated with continuing to evaluate that vaccine and other vaccines, while also making sure that people are not taking vaccines that might actually harm them.

And so it is a difficult balance to figure out exactly where that is. And it may be -- as you know Marion did put forward the expanded access regulations as one approach that could be used. One could

potentially contemplate an EUA for a rather limited population. But of course one doesn't want -- if there's a vaccine that appears to have high efficacy or appears to be capable of saving lives, one doesn't want to stop that vaccine if there's a significant chance that it will save lives because that's part of the public health calculus as well. So I will stop there.

DR. MONTO: Thank you, Dr. Krause. I think we're going to have to move on. We've got a lot of people who want to make comments. I think what we have to do is keep focusing on EUAs versus BLAs, formal licensure, and not really try to talk about sterilizing immunity or other things which are not part of standard vaccine licensure.

Most of our vaccines are licensed to prevent laboratory-confirmed disease and those diseases are different depending on what they are. And we rarely get into looking at a definition of serious disease and as Dr. Krause said, things that prevent infection and laboratory-confirmed infection typically prevent

serious disease and maybe do a better job at that. Dr. Cohn.

DR. COHN: Hi. Can you see me?

DR. MONTO: Yup.

DR. COHN: Okay. I just want to make a couple of comments. First of all, I really appreciate the balance that FDA is trying to strike. I think they've captured the challenge between ensuring a safe and effective vaccine and not withholding a potentially safe and effective vaccine from use. I want to make two points.

One is that I am actually less concerned about, for example, adverse events in the 30,000 participants in the clinical trial after the two-month follow up as I am potentially about more rare adverse events. And anything in terms of prolonging or thinking about waiting longer isn't, from an EUA perspective, won't change that. But this is why we have our safety surveillance post-authorization needs to be so strong and effective so that we do identify

potentially more rare adverse events than you would identify in a trial with 30,000 individuals.

The second point I want to make is that I do worry a little bit that the VE estimate for mild disease may be overestimated when we're just looking at the first two months after vaccination and that we may have a lower VE estimate, for example, if we looked at the data after four or six months just because of waning immunity.

Very rarely do we look at VE so shortly after completing the series. And so I don't think it's a factor that would lean me towards not agreeing with the 50 percent. But I do think it could be a potential communication issue if it hovers on that 50 percent point estimate after two months and then it falls much lower when we actually look at the data for BLA.

DR. MONTO: Which is why we have to continue to keep the randomized design. Right? Okay. Is the next one my -- I've gone off --

MR. KAWCZYNSKI: Yeah. The next one we have

is Paul, Dr. Paul Offit. I'll unmute you.

DR. ANNUNZIATO: Hi. Thank you very much.

DR. OFFIT: Paul or Paula?

DR. ANNUNZIATO: Oh, sorry. Not me. Let me seed my spot to you.

DR. OFFIT: Oh, okay.

DR. MONTO: I think that's actually a song, isn't it? Wait, did I just lose -- with me, go back to this --

MR. KAWCZYNSKI: Dr. Offit?

DR. OFFIT: Yes. I'll be quick.

DR. MONTO: All right. There you are.

DR. OFFIT: So just, it is disappointing, I think, that given that this is a vaccine that's being paid for by the public -- I mean BARDA is public money -- that the FDA can't direct this vaccine to make sure that we are testing it in groups like those who are at greatest risk, the various racial or ethnic backgrounds, health problems or age. That said, I mean, I'm on the NIH Active Group, which was put

together months ago by Dr. Collins. And on that group were members of the industry, Pfizer, Moderna, Merck, and those people were on that working group. And so when we -- when Larry Corey, who headed the clinical trials subcommittee, was putting together how he wanted these trials to be done, this was key.

I mean, we did not want this to be a study of, you know, healthy young white people. We wanted this to be a study that represented the American public at greatest risk. And my sense from those discussions is that is exactly what they're going to do. So I don't -- I understand Dr. Hildreth's concern but I think when this is -- plays out that we're going to find out that these are represented, groups. And in fact, one of the company's actually slowed recruitment because they weren't getting enough in the way of minorities. So I don't think in the end this is going to be a problem, but we'll see. Thank you.

DR. MONTO: Thank you, Dr. Offit. And I've heard there are also lots of outcomes. Dr. Annunziato.

DR. ANNUNZIATO: Okay. I just wanted to make a point that, you know, vaccine researchers and developers, manufacturers, public health entities, and so many others have really collaborated in a very focused way in order to try to deliver safe and effective vaccines in this very short period of time after the emergence of this virus. And I think, what I've heard today at least, is that there's broad concern that the speed of this response has been at the expense of careful scientific methods and we need to continue to work to address this perception.

That being said, I myself find that the thoughtful consideration and the clear guidance that the Agency's provided in these two guidance documents on the regulatory requirements for full licensure as well as for EUA will in fact help us as manufacturers and sponsors develop COVID-19 vaccines that will be held to the highest standards as we've heard today.

And so I, in fact, want to commend, you know, our colleagues that we've heard from today from the FDA

for their, you know, timely and careful consideration, understanding -- as it's been said -- we're trying to fly and build this plane at the same time, and that nothing will be perfect. I do think that these guidance have struck a key balance and should be supported.

DR. MONTO: Mr. Toubman.

MR. TOUBMAN: I also appreciate the difficult balancing that has to go on here and all the work that folks at the FDA have (audio skip). I'm coming, obviously, from the consumer rep's point of view, no technical background, so all I have really is, you know, I try to follow up on what's been going on and common sense. But also, I'm very affected by the public perception because in this particular case public trust equals success. Lack of trust means no success. That seems pretty clear. And where that leads me to is a conclusion that EUA probably should not be used here.

And I say that because, first, start with the

fact that EUA is almost always used, I think there's one exception, for people who are sick and you're basically putting something which is not fully tested but they are ill and so it makes sense you have to do something. And the balance changes there. Vaccines is a different story. But almost everybody's going to be injected is going to be healthy at the time they get the injection, so I think that has to be factored in anyway.

But on top of that, we have serious vaccine hesitancy. And now we have, as the speakers made clear, and really I greatly -- I think we all appreciated the Reagan-Udall Foundation data and information because basically what we're hearing is that the perception is that this is the speed and it's a result of political pressure and that's what it's really about. It's not about the science. It's not true. But that is the perception.

And so anything that sounds like emergency use authorization, you know, it sounds like it's being done

rushed and it's not the full review so even if it were -- even if EUA standards were similar to full licensure it doesn't sound good to the public. And again, what it sounds like matters. But here there is a difference and that -- and there are several differences. But one is that the primary one is duration, is that it would be median two months. And whereas -- and I understand that full licensure is probably like six months. So there really -- that duration makes a difference in terms of both safety and efficacy.

And you have to note for that -- for the second question, sorry I'm jumping ahead. But the problem of people bailing from the test if you go -- if EUA's granted what happens is people in the placebo, you know, they move towards getting this thing anyway. So those are a lot of problems with an EUA in this particular situation and that's before we get to the problem of likely poor participation by people of color in some of the studies. Although Moderna, it sounds like they've done a great job there.

I think that what Corey said it really sums it up for me, which is there's only one chance to, you know, to do this and do it right. If we do it wrong, then we're done for. It'll be years because the -- there's already a serious problem of lack of trust. The trust will become so severe at that point that we won't be able to dig out of it.

So given all of this and that public (audio skip) -- sorry. I was muted for a second there. I would recommend that we not do EUA here but if we're going to do it, I would suggest the following: That it be for a longer period. Not two months, maybe three or four months. And two other things, if we are told that the primary endpoint can't be determined, and I'm surprised by that, I agree with Dr. Hildreth that looks worth looking at if the taxpayers are paying we maybe should be able to identify the primary endpoint. But in any event, it could the basis for EUA. If you're going to get EUA then the primary endpoint has to be something more serious in terms of serious disease.

And lastly, again, if we can't determine who are the demographics of who's actually in the study we could say if it turns out that the demographics were not good then we're not going to grant EUA because of the risk. Whereas, if a company like Moderna, I guess, has really good participation that's representative that might be a reason if we're going to approve the EUA. But I would be very, very reluctant to do it under all of these circumstances, and particularly the public's hesitancy over this particular project. Thank you.

DR. MONTO: Dr. Krause, I see you have your hand raised. Was that from before? Even if you -- if it was from before maybe you could comment about the term EUA. Is there anything else it could be called? Thinking back to other issues. And we also heard about longer than two months. Seems to me that if we answer positively, we can figure out how to continue the randomization. It doesn't really matter that much whether it's two months or four months. Are you

available?

DR. KRAUSE: Yes, sir. I am. So my hand was up from before. I took it down now. But -- so, you know, we're obviously working within the framework of the regulations that we have. And so the emergency use authorization is one of the things that we can do, and expanded access is one of the things that we can to and BLA is one of the things that we can do. One of the problems with the Emergency Use Authorization is that it's positioned in this way that is on the one hand close to BLA where we would like to have fairly high standards for it, and yet the EUA also does, in fact, represent an investigational product. It hasn't yet met the standards for licensure. And you've heard some of the data differences which include follow up.

But I don't want you to underestimate the importance of the FDA review that goes along with the BLA too. Because under BLA the FDA has actually carefully reviewed essentially every single person who's been in those trials and looked at what happened

to them, and has carefully looked at the manufacturing process, and all the ways in which the manufacturing process is controlled to make sure that this product can be consistently made. And so although, if there were an EUA the standards would be very high, as you've heard, there is no way that they could be as high as they would be for a BLA.

DR. MONTO: And it is possible that something which is -- a product which is given an EUA may not receive a BLA because they can't meet those standards.

DR. KRAUSE: Well, the hope would be that if it got an EUA because it had at least the clinical data that would make it likely to meet the BLA standards initially that it would receive BLA. But of course, it's conceivable with additional follow up, or with the active safety follow up that FDA is also requesting during a period of an EUA, that something would be uncovered about that product which would make one not want to license it.

DR. MONTO: Right. That's what I mean.

DR. KRAUSE: And that's why the EUA product is investigational. It's not a guarantee of a BLA. And yet we would hope that products that are made available under EUA would subsequently qualify for BLA.

DR. MONTO: And as you plan any issuance of an EUA will also have a committee review.

DR. KRAUSE: That is absolutely correct. And that's in the guidance and we've heard both Dr. Hahn and Dr. Marks commit to that as well.

DR. MONTO: So that we'll have this second chance to go over the specifics. Once we agree to the principals that have been put forward today in the guidance.

DR. KRAUSE: That is indeed correct.

DR. MONTO: Okay. One more hand raised and that's Dr. Perlman.

DR. PERLMAN: Yeah. I just want to add to the idea that we should -- that we might want to prolong the two months to a few more months for a few reasons. First, from what we know about common coronaviruses and

immune responses we know that at two months is probably a good immune response and that it wanes between six and twelve months. There's plenty of illustrations of reinfection. Whether vaccine's going to be the same, of course, we don't know.

But as you have waning vaccines you might have more chances to have any adverse -- not adverse effects, but rather vaccine problems -- vaccine-related problems that wouldn't be seen at the two-month mark. In a way, two months would pick up a lot of the early adverse events, but I think it's a continuum. We certainly know the measles vaccine wasn't picked up as a problem until it killed one and took two to three years.

And we're not going to go that long, so there's a continuum and it's kind of a -- to me, in my mind, it's an arbitrary point of where you do things weighing everything together. But if you do a few more months and if this behaves like the responses to the common cold coronaviruses, we might have a chance to

pick up these vaccine-related problems that we might not see at two months.

DR. MONTO: Well, that's going to be followed if we keep the randomized trials going.

DR. PERLMAN: Got you.

DR. MONTO: Which is --

DR. PERLMAN: Which would basically --

DR. MONTO: The next --

DR. PERLMAN: -- really the big problem --

DR. MONTO: -- point.

DR. PERLMAN: Yeah.

DR. MONTO: So before we go on to number two, which again is related I just want to summarize what I've heard. And that is, there is some concern about the period of two months as being somewhat arbitrary, but recognition that the study will still be going on if randomization can be continued at least in a large subset of those that are being studied or receive the EUA. That we want to be sure that minorities are represented and then, and this is a little bit outside

the scope -- concern about immuno-bridging to children, that there's only one trial that goes down to age 12. And because of issues of immune response, et cetera, and MIS-C there is concern that it may be an inappropriate to use standard bridging guidelines.

Saying that, let's go ahead and try to talk about the very thorny issue of continued blinding of Phase 3 clinical trials if an EUA has been issued. I know that in one of the letters we received from one of the manufacturers it said that anybody who is eligible to receive the vaccine under EUA who has been in the clinical trial will, for ethical reasons, be offered -- and in the placebo group, will be offered vaccine which breaks the blind.

Let's have a more general discussion of this issue because one of the reasons why we would feel comfortable with getting the EUA issued after two months is that there will be continued follow up to see if there's waning of immunity, to see if there are side effects over a longer period of time. So I'd like some

contributions about -- clever ideas about how to continue observations even though an EUA is issued.

And I think there may be issues also about how much vaccine is available at the issuance of the EUA, and the fact that certain population groups might be included in the EUA, and other groups would still not be able to receive vaccine under the EUA and therefore could be continued in the randomized trials. So Cody Meissner is up next.

DR. MEISSNER: Thank you. I -- if -- yes. Thank you. I just wanted to make one comment about why the two-month interval I think was selected in terms of follow up for the vaccine. It's a tie-on to the last discussion. But most adverse reactions occur within the first six weeks following administration of the vaccine.

For example, Guillain-Barre syndrome when that's followed an influenza vaccine to have occurred within that four to six-week window. So I think that's the basis for selecting eight weeks. I agree, it's

short for vaccines with a new platform, but I don't think it's a completely random selection. So that was just a tie-on.

Then, in terms of --

DR. MONTO: Exactly.

DR. MEISSNER: I'm sorry?

DR. MONTO: I said thank you for that. I think that's a very important observation and why the two months was chosen. So please, go ahead.

DR. MEISSNER: Thank you, Dr. Monto. I -- and then the question I have on unblinding is, was this addressed -- this issue addressed in the informed consent that everyone must have signed? I can't imagine that the informed consent didn't address the issue of what would happen if there was a conclusion. And so I think, isn't -- that should be stated.

DR. MONTO: Very interesting point. Most informed consent say that people can withdraw at any time anyway. So is there anybody who can respond to that? Dr. Krause.

DR. KRAUSE: Yeah. So in general in these trials, there's not built into the trial protocol, cross-over. And so there has not been any promise to the people in the trial that they will be eligible to receive a vaccine when it becomes available. And, of course, if they were to become eligible the question would be, when? If the EUA came about as a result of an interim analysis, would that be the time at which one would do that, or would one wait until the trial had actually finished?

The vaccine then might be -- one had more data, and the vaccine might be available for licensure. But to answer your question, there isn't a priori any promise to the people in the trial that they will receive that. And so presumably that kind of a promise was not required to induce, obviously, the volunteers who I think generally joined the trials out of a sense of altruism and a desire to help. But -- so to continue them on placebo wouldn't break a deal.

I'll make one other point and that is that

vaccine recipients -- placebo recipients otherwise likely wouldn't be the first in line to get a vaccine. Normally you would think about the first in line even as a vaccine became available would be those who are at greatest risk, or perhaps members of under-represented minority groups and so forth. And if anything, the average trial recipient might actually be at a lower priority than certain other people who might be in line to get a vaccine.

And then, of course, third, not prioritizing placebo recipients to get vaccine once it became available, even if a vaccine is 100 percent effective doesn't put them at enormous risk. Obviously, everybody is at some risk, but everybody also has other ways to protect themselves. And even if these people were kept in the trial for some additional period of time, many of them will surely get the vaccine long before other people do just because of the likely availability and the roll-out of vaccine.

And in fact, we heard this morning in one of

the presentations that many people will want to wait at least six months before a vaccine is made available before they would take it anyway. And so that's sort of -- is an argument also that there may not be a clear obligation to people who are in the trial to give them a vaccine even if they were originally randomized placebo once there was an EUA. So I'm sort of summarizing these. These are arguments that I've heard.

I'm not myself an ethicist but I have heard discussions about this as --on this general topic and these are some of the considerations that are brought forward in thinking about this, make the argument that there wouldn't necessarily be a strong reason why one had to do it. So for those who say there's an ethical reason, I think that that's perhaps overstating the case.

DR. MEISSNER: I --

DR. MONTO: While you are there, Dr. Krause, can I ask you whether an EUA could be issued for

healthcare workers or first responders, or groups like that? That's usually something that's handled by ACIP.

DR. KRAUSE: So I think we would have to figure that out. It's difficult. One could contemplate a very limited EUA based on a perception of what the risk was, for instance. Because EUA is authorized based on a benefit/risk calculation and so if, when we were to say well, we want to make this vaccine available to people who are in the highest risk group, one could try to cut it that way. I think it might be harder to do it based on other factors than risk. Although, you know, that's not something that we've in the past done.

There's only been one vaccine EUA in history and so exactly what we are able to do there is unclear. Of course, on alternative might be to -- if vaccines become available early to use them under expanded -- not become available, sorry. If an interim analysis suggests efficacy, one could start with an expanded access, and then as one gathered data then perhaps move

to an EUA. But of course, there's some complexities there also. Under expanded access one surely would have very high degree of control over who could get the vaccine.

DR. MEISSNER: Was that the anthrax vaccine you're referring to in terms of a previous EUA?

DR. KRAUSE: Yes. Yes, it was. Yes.

DR. MEISSNER: And that was a little different, right, because it was outdated vaccine for first responders.

DR. KRAUSE: Primarily for the military actually.

DR. MEISSNER: Yes.

DR. MONTO: Okay. Thank you. Dr. Pergam.

DR. PERGAM: Yeah, thanks. I wanted just to emphasize one of the points that you made, Arnold, is that I'm not sure how much vaccine's going to be available. And so this is really going to be part of the EUA thought process is, making an EUA available does not necessarily indicate that we're going to have

a ton of vaccine that we're going to be able to give to people. And that sort of makes you wonder, again, what's our goal here?

So I think we're going to have to specify what groups potentially -- I'm not sure we can do that as that's been described it may be an ACIP issue, but if healthcare workers are first, you know, in line definitely to get vaccine that would make sense. What I'd really like to know and what we didn't get a chance to ask, was the Reagan-Udall group a little bit more about -- they did these analyses of two different populations, the general public, and healthcare workers. It would be really curious to know how healthcare workers felt about getting an EUA vaccine versus one that has been fully addressed in a Phase 3 trial. Because I think they're necessarily going to be people that are more educated and may want to wait until it's been finalized.

And I also have to say that healthcare workers in general, while they are a high-risk group because of

exposure, the data does not suggest that they're the ones with the most disease by any stretch because they're the ones with the most PPE. And so I worry about the perception that might come across with that.

DR. MONTO: Right. So I think that's the problem with healthcare workers. If they have EUA -- if they have PPE the infection rates are very low. But I just put them out a group that's usually listed as being at risk. Next, Dr. Notarangelo.

DR. NOTARANGELO: Thank you. Thank you, Dr. Monto. Well, it seems to me that continuation of blinded Phase 3 clinical trials is absolutely critical and so we should do all what we can to make sure they continue. I think, you know, some of the ideas that have been proposed by you and also emphasized by Dr. Krause are, I think, what we should be doing. So if we issue an EUA -- if we agree on the issue of an EUA, at that point I think the next step would be to have a prioritization of which groups would be entitled to receive the vaccine.

And, you know, healthcare workers may not be the right population but perhaps nursing homes, people running nursing home might be a good population for testing. That would allow, basically, us to gain time so that we would have continuation of blinded Phase clinical 3 trials to accumulate all of the data that are required for full licensure. I wonder whether we can also, you know, invite the FDA to initiate a conversation with ACIP.

I mean, there was, I think it was the Infectious Disease Society representative that proposed a joint action with ACIP and that might be something to consider. But along that line, I think, you know, EUA issuance would not necessarily prevent continuation of blinded Phase 3 clinical, trials and I think that would be important.

DR. MONTO: Dr. Chatterjee.

DR. CHATTERJEE: Yes. Thank you. So just a couple of points. One is a follow up which is with regard to who will get this vaccine and how quickly

will they get it. As best I understand it, and I'm sure that the sponsors know this in terms of who in their trials, the likelihood that there are a bunch of healthcare workers or first responders who are in their trials I think is fairly small. So, you know, in terms of losing people from the trials because they're the ones who've been prioritized to receive the vaccine earlier on, I think is less likely to happen.

The other thing goes back to a couple of people mentioned this already, which is how quickly do we get this vaccine out to people? You know, it may be actually, even with all the kitting and everything that's being done to position the vaccine to be pushed out as quickly as it's authorized and licensed, it's probably going to take several months before the vaccine gets into people's arms. And so there will be this lag, there will be this delay during which the data will continue to be accumulated. And so I just wanted to make that point.

The second one is with regard to waning

immunity and what happens two months out versus six months out. I wish I could quote you the data, but as probably everyone on this call is aware, the early weeks is going on right now. And I saw a presentation yesterday on seroprevalence studies and, you know, what happens to -- with natural infection, what happens to the immunity. And it seems like, yes there is a waning but then there's a plateau that goes on for several months.

And of course, not having a serologic corridor protection we don't know whether that's sufficient to protect people from infection or from disease. But it certainly doesn't look like it sort of goes up and goes down and disappears.

DR. MONTO: Yeah. Waning is something which our group has been studying very carefully with influenza vaccine and you're absolutely right. The waning occurs quickly right after vaccination and then sort of plateaus going out and we really do not understand with coronaviruses what the -- what will be

the case, and I think we just have to learn about that as we go forward. One of the questions that we can never ask -- answer about a vaccine when it's licensed is how long it's going to last and whether we're going to need boosters. So let's go on to Amanda Cohn.

DR. COHN: Hi. I want to go back to the question about the unblinding. And it feels like I agree with everything Dr. Krause said. But it feels like there's a difference between actively unblinding and offering study participants vaccine versus an EUA being available and somebody potentially being in a recommended group to get the vaccine, and them making a choice to go get the vaccine but maybe not knowing -- I -- what I'm trying to say is that I wonder if all the study participants understand that they did potentially get a placebo. And if there's something that you could do to sort of make study participants aware that if they are in a recommended group, they could consider going to get vaccinated while not unblinding the results, if that makes sense.

I do worry about telling a person that they should not go get vaccinated when they are in one of the prioritized groups, potentially. I also agree that there will be limited doses early and there won't be that many participants in the study who will be recommended for vaccine early.

DR. MONTO: Thank you. Mr. Toubman.

MR. TOUBMAN: I -- so Dr. Monto I have a question for you first because I'm confused by something. You had said that one of the companies --

DR. MONTO: I'm probably just as confused. Go ahead.

MR. TOUBMAN: I believe you said that one of the sponsors had sent letters to all the participants saying that --

DR. MONTO: It was to the committee. To our committee. It was sent to our committee.

MR. TOUBMAN: Okay.

DR. MONTO: It's in the file -- the box file that we got.

MR. TOUBMAN: And what did the letter say since I'm not going to look it up right now?

DR. MONTO: The letter says that for ethical reasons they may have to tell the placebo recipients that there is an EUA available vaccine which they can receive.

MR. TOUBMAN: Okay. So here's the thing that occurs to me. It was pointed out by Dr. Krause and others, there may not be enough vaccine anyway, so if it becomes a choice it's not a real choice. But the problem as I understand it is if those people, even though they can't get it now know that they're in the placebo group their behavior may change. That's the whole reason for having a blind study.

DR. MONTO: Exactly. They --

MR. TOUBMAN: Nobody knows if they're protected or not so they all act -- both sides act the same and you basically destroy that if you inform them.

DR. MONTO: I probably shouldn't have brought that letter up. It was in our file and I had some

questions raised by it because of the potential for unblinding which destroys the whole purpose of a randomized trial. But I think we can worry about that when -- if and when that company's product comes before us.

So I apologize for bringing it up. But I just wanted to point out the complexity of this issue and that we should be pretty firm about what we want and what we are unhappy with in terms of continuing the blinding.

MR. TOUBMAN: All right. And obviously, this goes back to the earlier question, but this is a problem. There's no question that we've got a problem here if we do EUA under these circumstances and that's where we should be careful. And by the way, I did appreciate Dr. -- Cody, talking about why they picked two months. But that's the reason why they chose three months because in the past it's generally been six weeks but with new platforms, we don't know so I'm just -- I'm confused why we're not being willing to be open

to extending that period to what the WHO uses. I'll save that for later, I guess. Thanks.

DR. MONTO: Okay. Dr. Nelson.

MR. KAWCZYNSKI: Dr. Nelson, you're on mute, sir. Dr. Nelson, can you say something?

DR. MONTO: It's so complicated for him.

MR. KAWCZYNSKI: I think we can hear you now. Go ahead and say something, Dr. Nelson.

DR. NELSON: How about now?

MR. KAWCZYNSKI: There we go. We got you.

DR. NELSON: Yeah. So I had to log back in and apparently, my phone number got disconnected from the video.

MR. KAWCZYNSKI: You're good.

DR. NELSON: Dr. Monto, I did want to make a point regarding your concluding summary for question number one for the record. There was a lot of concern about the primary endpoint being in favor, or at least enabling the potential for milder disease, and I hope you captured that as part of the conclusion of the

discussion. With respect to this particular question, number two, I think it is important to make the distinction between continued monitoring of placebo recipients versus ongoing enrollment and the potential for new placebo recipients to receive vaccines.

Two very different scenarios in the presence of an EUA vaccine on the street. And I would highly recommend, since they're asking for recommendations for guidance to industry, that we would ask that those that continue to enroll once an EUA is on the street have a specific plan for when placebo recipients will, at some point, be enabled to receive a vaccine to protect them from this disease.

DR. MONTO: Dr. Annunziato.

DR. ANNUNZIATO: Hi. Thank you very much. I wanted to address some of the points and questions that Amanda Cohn and that Dr. Nelson had brought up because we, and I know others, have -- do have experience conducting placebo-controlled trials for approved and available vaccines. And there are a couple of critical

considerations that you really need to keep in mind when you're doing studies in this way.

So of course the trial objectives need to address important clinical, scientific questions. And that's the situation that we're talking about here. And as part of the informed consent process, participants have to receive clear information about the availability of an approved vaccine for them and that they can receive the vaccine outside of the clinical trial that they're being asked to participate in, that they may receive placebo or an unapproved vaccine if they join the study, and how long they're being asked not to be vaccinated with an approved vaccine that they're otherwise, you know, could access.

And when I say the informed consent process, this is something that happens, as you all probably know, not just when a subject or a volunteer first joins the trial. But as the scientific knowledge and the availability of vaccines or treatments evolve during the conduct of the trial, the consent process

needs to be, you know, done again so to say, subjects are reconsented to make sure that they're aware of the most current information.

So, you know, we think that these principles would apply if a vaccine were to be granted an EUA or a full approval for COVID and -- but we really need to also think about the feasibility of conducting placebo-controlled studies if in fact there is a vaccine available to the general population, or even to specific segments of the population by an EUA.

So this is really going to depend on the specific, I would say indication, but maybe it's really the recommendation, you know, how the EUA approved vaccine would be administered, who would be able to access it, whether or not all the countries that are participating in your trial have approved vaccine provisions as well, and the availability of the vaccine, you know, to the different specific groups who are in your study.

There are a couple other really unique aspects

to this situation that have really struck me in listening to people talk today that's going to create additional challenges for investigators and sponsors of these studies. And these might not be actually overcome-able. We'll have to see and think carefully about it. But the great public attention that's being given to this vaccine, to these vaccine development programs, and the strong perception that you know, based on a variety of concerns may in fact preclude continuation of some of these placebo-controlled studies.

We'll just have to monitor and watch this carefully. In fact, if vaccines do become available to the entire U.S. population, I think we heard earlier today that the projections are that, you know, by next summer that may in fact be a reality. And so as I said, you know, this is something we'll have to monitor and watch. But just in general, you know, typically you are able to continue your studies under these circumstances.

DR. MONTO: Thank you. I just wanted to remind us all that we have been using observational data for a lot of effectiveness studies. So what looks like logistically difficult, maintaining the blind for very long periods of time may not actually be -- both not feasible and not necessary as we go forward. And that's why we're shortly going to get into question number three which really looks at other kinds of observations. I see one more hand raised. Dr. Kurilla.

DR. KURILLA: Thank you. Yeah. Just wanted to make one comment -- follow on a couple of other comments with regard to the unblinding. And it's my understanding, Dr. Krause can correct me if I'm wrong, but I don't think FDA would be issuing an EUA for specific populations such as healthcare workers or something like that.

I would assume that they would be issuing an EUA based on the data for the specific populations within the trial protocol upon which randomization was

done. And I know, for example, having read one of the protocols that the randomization was done on individuals under 65, under 65 with comorbid conditions; and there was a list of those specific ones that would put them in that "high-risk category," and then over 65. So those would be, I would assume, the available data sets upon which an EUA would be based.

Now, just because an EUA is issued for people under 65 doesn't necessarily mean that everybody under 65 gets it. There isn't going to be enough vaccine in the first place. But that's where a group like ACIP or other entities are going to have to make a decision on what risk groups based on exposure, as opposed to just based on their particular characteristics from the trial design, would specify. So I don't think that it's going to really be a major issue in terms of preventing the ongoing conduct of the Phase 3 trial.

DR. MONTO: Especially if the vaccine is available in relatively short supply. Dr. Krause, did you have anything further to say before I attempt to

summarize, which is going to be rather difficult?

DR. KRAUSE: No. That's fine. Thank you very much.

DR. MONTO: Okay. So we all wish we could continue unblinded -- or blinded collection of data but we realize that there may be some problems. We talked about various scenarios that might be used. And this is something which we would like to see but if we cannot, then we move into follow up studies on -- in an observational setting and therefore we will go into question number three.

Please discuss studies following licensure and or issuance of an EUA for COVID-19 vaccines too and firstly safety, efficacy, and immune markers of protection. And I -- let's leave out immune markers of protection because that's a whole different issue. So let's just look at safety and effectiveness.

MR. KAWCZYNSKI: All right. The first person we have in there is Dr. Gans.

DR. ALTMAN-GANS: Thank you. As I mentioned

when I was talking about one, which kind of overlaps because it's the same safety things, I did just want to put in a plug for in terms of safety, there's a couple things that I think are problematic. The first one is that the solicited safety profiles only through day seven. I think that's problematic and should probably extend longer than that, but this post-marketing anyway.

The post-marketing I think from what we heard earlier is a little problematic in a couple of things. So the first line people who may be issued this, we heard about healthcare workers, we heard about certain populations. And a lot of them are not going to be included in the databases that are currently being used to monitor these safety events as we go through, particularly the non-passive ones. So (inaudible) is obviously anybody. And so that's really problematic.

The problematic issue is also going to be a lag in time. So the number of doses that have to be administered to actually get a signal on BSD or

something like that is actually problematic. Again, given the people who are likely to get it first might not be in those systems. So I think we need to be more dynamic and more flexible in how we think about these.

I also think we're not utilizing our new platforms. So there was some talk about using the signal system and using BAPP, but it wasn't clear from the presentations that they're actually looking at these. And then using some kind of phone platform where people can also self-report. So I think all those have to be actually incorporated into what we would see in terms of the safety signals moving forward. So I think those are going to be very important.

I would say that in terms of safety we also have to add some other kinds of markers. I'm not going to talk about the markers of protections because I think they're going to do all the B-cell and T-cell studies particular to SARS-COVID-2. I think that's fine and we'll learn something perhaps from that. But

the markers that I am particularly interested in are in the pro-inflammatory and pro-thrombotic, which I think need to be part of an ongoing safety signal that would part of that. And I think that's all I wanted to add there.

DR. MONTO: Dr. Chatterjee.

DR. CHATTERJEE: Yes. Thank you. So just a couple of quick points to make. With regard to safety, I think, you know, particularly studying sub-populations would be important in making sure that this -- whatever products get licensed or authorized are actually safe in the populations that they might be used in. So that would be one.

The other is the longer-term follow up could be maybe more months to years that might be necessary to identify safety signals that might not show up immediately. And with regard to effectiveness, it's similar kinds of things, particularly as we talked about, you know, the effectiveness against severe disease, and in those populations that are

disproportionately affected, as well as how long the immunity actually lasts.

And then with regard to the specific populations, we've talked about this already. For children, I think in terms of immuno-bridging for effectiveness, even though we don't have a serologic corridor of protection but if it appears to be protective in adults perhaps we could look at that. But the safety issue is a very different animal, I think. And I think the studies do need to be done in children to assure that these products will actually be safe for use in children.

DR. MONTO: Thank you. Dr. Notarangelo.

DR. NOTARANGELO: Thank you. So, Dr. Monto, first of all, I would like to endorse your proposal; and not to talk about enhanced respiratory disease but to comment on enhanced disease that would include also all of the vascular thrombotic events that were mentioned before. My other comment is about children. As you heard from my previous comments, at this point

I'm not particularly eager to have children as potential candidates for receiving vaccines.

I don't think we have enough data there and I don't think we can use the argument of immuno-bridging because I might see something that's very specific to SARS-COVID-2. We cannot take lessons from other vaccines in that regard. But, in any case, if children at some point are included in the absence of trials or specifically targeted to children we would need to have safety studies that are long enough in duration to include the potential appearance of MIC and they should be large enough to take those into consideration. Thank you.

DR. MONTO: Dr. Pergam.

DR. PERGAM: So one thing we'll definitely be curious when the EUA get presented to us, the possibility is certainly for a lot of these trials, the Phase 1 and Phase 2 data, will have longer-term follow up I would hope. Although I haven't heard that from the companies specifically to determine whether those

that were in Phase 2 and Phase 1 trials were followed for prolonged periods to see about waning immunity. Because that could be really interesting information. Even in a small population, it might help us to think about these EUAs. Even with a smaller group and differences in how the vaccine was given, I would be curious to see if that data is going to exist within those patient populations.

And I'm still unsure about the EUA that some of the correlates that they're going to be looking at in these patients. Is there a possibility if an EUA is developed that there can be a requirement for monitoring a new patient similar to what they're doing? I think it was the phone-based app, is the V-Safe app that if they did do an EUA and we had some of these individuals vaccinated, one thing I think we are potentially losing is the ability to follow them closely for potential side effects.

DR. MONTO: Well, I can't answer for Phase 3 commitments. What I can tell you is that I know that

CDC and other agencies are thinking, design your studies to look at long-term effectiveness which will give you answers about duration of immunity. I think there's also the issue of enhanced disease at -- if there is break-through infection and that could be an infrequent complication which you will need the larger numbers you get in observational studies to pick up. So the observational studies are going to be very important for safety as well. Dr. Meissner.

DR. MEISSNER: Thank you, Dr. Monto. I would just like to state the fact that I agree with Dr. Notarangelo and apologize if I didn't pronounce that properly but in terms of studies in children. I think it's going to be so important to evaluate any vaccine in children and adolescents before they're included in any sort of a recommendation. I think the rates of disease are nowhere near as high as they are in the high-risk groups, such as individuals over 60 or 65 years of age, they're only a fraction. And we know that MIS-C occurs at a rate, as I think I mentioned

earlier, of 2 cases per 100,000. So I would, if I were part of the FDA, I would certainly want to be very convinced of the safety of a vaccine before I recommended or approved its use in children. Over.

DR. MONTO: Thanks. And that's a message we've heard before. Dr. Gruber.

DR. GRUBER: Yeah. I just wanted to clarify for the committee that in regarding studies in children that there is actually a law, the Pediatric Research Equity Act that requires manufacturers of vaccines and other products to conduct studies in children. Of course, we can license a product if we have a -- if the safety and efficacy is established in adults and we would not have to hold up licensure.

But the vaccine manufacturers really have a, you know, and that's mandatory. They need to submit a pediatric study plan. And they are -- they need to outline the studies that they plan to conduct in children. And so we will be getting data on safety in the subject population. I just wanted to clarify that.

DR. MEISSNER: Thank you, Dr. Gruber. I, as a pediatrician, completely concur on the importance of including children in the clinical trials. But I think they need to be evaluated as a distinct group with phased evaluations just as is being done in adults because the pattern of disease is quite different in children and I -- lumping them in with adults in this -- with this particular illness I -- would cause me some discomfort. Over.

DR. MONTO: Dr. Kurilla.

DR. KRAUSE: Thank you. Yeah. The few comments regarding safety, I think we need to recognize that there's a lot of new platforms here that are being utilized. And so rather than our traditional, let's do vaccine by vaccine, I think there needs to be a concerted effort to see whether or not there's some long term effects or impacts overall on the health of people with regard to specific platforms or -- and or novel adjuvants that may be included. We need to try to -- we need to have a systematic way of not just

looking at it at a vaccine by vaccine basis. But that's one aspect.

You know, with regard to children in particular but I think in general, you know, it's been mentioned before, we don't have a correlative protection. And I think it's also rather interesting and rather paradoxical finding that individuals with low -- with mild or even asymptomatic infections tend to have low serologic titers in response to the infection. The degree of antibody titers seems to be positively correlated with the severity of infection, which suggests either that the asymptomatics are having a very rapid antibody response that goes away quickly, or they actually have an antibody independent response that is mediating the host defense.

That may be going on in children more so than in adults and I wonder if that we're -- it's not that introducing neutralizing IGG cannot work as a vaccination strategy, but I wonder the potential that we may be circumventing a more natural response to the

infection may have some downstream impacts. So I think we need to be a little cautious about that until we really start to understand the correlates of protection from natural infection so we can relate how that impacts what the vaccines are doing.

DR. MONTO: Thank you. And the reason I said I didn't want to talk about immune markers of protection is that I think that is a very complicated issue and it's not only going to be -- we're not going to learn only from breakthrough infections and things like that in the vaccinated but also from natural infection.

As we -- since we're getting pretty late and we have point B, I want those who have their hands raised to try to bring in also the issue of specific populations. I'm not sure that we haven't gone over this already so it may not be necessary to handle it separately, but I do think that we want to cover that as well. And we do have -- we're coming up to -- we're getting close to our stop -- we're beyond our closing

time already and I really would like to stop before 7:00. So, Dr. Nelson.

DR. NELSON: I do think it's critically important that we do extend the study of those populations that are currently encouraged to be in the current clinical trial. In particular, the people of color and those disproportionally affected by infection itself. But also to take heed from some of the advice we heard from public testimony and from our own experience of noting that there are gender differences in immune response as well as safety and efficacy from vaccines. Those two particular ones.

But I think it's also important for us to remember who's not being involved in the current clinical trials. And all you have to do is look at the exclusion criteria of several of these trials. Those with allergic diseases that might be or likely exacerbated by vaccination, the immunosuppressed we did hear about earlier, history of primary malignancy or ongoing malignancy, bleeding disorders, uni- -- or

really multi-organ disease that is severe.

There are a lot of individuals out there who will be waiting for the licensure piece to have access to this vaccine, and specific study of immune responses of those critical populations I think is needed as well as safety. And if you look at some of those disease states it's also disproportionately affected by people of color and opportunities for us to generate real data and improve the trust in the vaccination process if we specifically study efficacy in those individuals.

One thing I haven't heard today is that we do need to generate specific data on vaccine co-administration. So it is critically important that we understand the interplay of this vaccination in the context of our routine schedule. And frankly, right now in the midst of catch up for all those who've deferred their routine vaccinations as a part of pandemic mitigations the last several months.

Another point I'd like to bring up, moving back to A is, I agree with Dr. Kurilla. They're new

platforms, there are new opportunities for rare adverse events. As an allergist, I was particularly intrigued to understand that two of the vaccines are relying on T-2 hypersensitivity immune responses. It may take several months for some of these exacerbations to come to fruition and show themselves through passive reporting systems. And the fourth point, I think we need to be very explicit in that there needs to be some intentional study of duration of immunity as part of these post-marketing surveillance studies. Thank you, Dr. Monto.

DR. MONTO: Thank you, Dr. Nelson. I think we -- what I would like to do first is to attempt to summarize what we've heard about the post-marketing, post-licensure studies. That these are absolutely necessary for duration of immunity or safety, particularly because we are using new platforms. That we should look at this not only by-product but also by platform because there may be commonalities to any untoward effects that are seen based on the platform,

as well as the product.

We absolutely need to have population specific data in terms of minority groups, women, men, and the rest. And the beauty of observational studies as vaccines are rolled out is that your numbers increase and you don't have -- if a vaccine uptake is there you don't have the numbers problems that you do, and the volunteerism problems that you have in the clinical trials. So we are all in favor of these kinds of studies, correlates of protection are going to be critical. Also correlates of natural disease.

This is something which is novel to our populations, at least SARS-COVID-2 is. Seasonal coronaviruses have been around for a while. We know a lot about them, but they -- we do not see the kind of pathogenesis that you do with this infection. So everything is on the table in terms of studies.

So I want to now since we're 10 minutes late as the evening progresses, I want to try -- close the meeting. I want to first thank the participants and

particularly the FDA staff who worked very hard. Virtual meetings are much harder to put together than together meetings when we're all together in -- at FDA. And I see Dr. Gruber -- before I sign off I want to thank particularly Mark Kawczynski who I -- who's done a yeoman's job in trying to keep me on because I am the worst actor in terms of an unstable system, which you may not have noticed because he's been so valiant in getting my back on.

DR. GRUBER: Thank you for giving me two minutes. I just wanted, before you adjourn the meeting and I know it is very late hours, but, you know, I want to also thank the committee for their very thorough discussion here. We know this is a very difficult and complex issue but if I can summarize real quick for what I've heard and, Arnold, you shake your head or you nod. Okay?

But in terms of the guidance documents and the approaches for safety and effectiveness data as we outlined them, I heard that the general principals and

the standards that we are applying are right on the money and that there is really buy-in for that. I hear there is some concerns and suggestions made for some of the details the importance for making sure minorities are included in clinical studies. We had some discussion from endpoints.

We can take this forward if we have, you know, new vaccines entering clinical studies. It may be a little bit difficult for those who are already in Phase 3. We hear you on the bridging issue with the peds population. What I want to know from you, the two months -- the median two months follow up that we said and the EUA as for people expressing some concern with that being maybe not short enough. But, you know, if it then cannot be longer by no means should it be shorter than two months of median follow-up. That's what I heard.

And in terms of the blind, I think that was keeping the blinded and the placebo comparator on even though you have an EUA. You said even though we all

would like for this to continue but we have to realize that at some point we can't really maintain the blind. But do I hear you saying, and do I hear the committee saying that the blind should be maintained for as long as feasible and there should not necessarily be an automatic cross-over of the placebo recipients to active -- to getting the vaccine?

DR. MONTO: I think that that is very clearly what you heard. I don't think there's been any doubt about that point. I think there may be some questions about the two months and also some of the outcomes that are being used. And as somebody who's worked flu vaccines for a long time, what you are using as the outcome is standard for most respiratory vaccines. And we learned about some of the other outcomes either as secondary outcomes in the randomized trials or in observational studies. So I fully agree with your summary.

DR. GRUBER: Thank you so much, Dr. Monto, and thank you again for the committee. Thank you.

DR. MONTO: Okay. So we are adjourned. Thank you all.

MR. KAWCZYNSKI: All right. Thank you. Thank you so much everyone and with that, this event has concluded, this meeting has concluded. Any additional questions can be sent the FDA OMA at FDA.hhs.gov mailbox. Thank you much.

[MEETING ADJOURNED FOR THE DAY]