FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
162nd Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN PUBLIC MEETING

VIRTUAL ONLINE MEETING

December 10, 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.

ATTENDEES

Arnold Monto, M.D.	University of Michigan
Paula Annunziato, M.D.	Merck
Hayley Gans, M.D.	Stanford University Medical Center
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	Centers for Disease Control and Prevention
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
Steven Pergam, M.D., M.P.H	Seattle Cancer Care Alliance
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Sheldon Toubman, J.D.	New Haven Legal Assistance Association
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A. Oveta Fuller, Ph.D.	University of Michigan
James Hildreth, Sr., Ph.D., M.D.	Meharry Medical College
Juan Gea-Banacloche, M.D.	Mayo Clinic
David Kim, M.D., MA	U.S. Department of Health and Human Services
Patrick Moore, M.D., M.P.H	University of Pittsburgh Cancer Institute
Jeannette Lee, Ph.D.	University of Arkansas for Medical Sciences
Stanley Perlman, M.D., Ph.D.	University of Iowa
Ofer Levy, M.D., Ph.D.	Boston Children's Hospital
Eric Rubin, M.D., Ph.D.	Harvard TH Chan School of Public Health
Pamela McInnes, DDS, MSc.	National Institutes of Health
Mark Sawyer, M.D., F.A.A.P	University of California San Diego

Ralph Tripp, Ph.D.	University of Georgia
Melinda Wharton, M.D, M.P.H.	Centers for Disease Control and Prevention
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Steven Goodman, M.D., Ph.D.	Stanford University
Nancy Messonnier, M.D.	Centers for Disease Control and Prevention
Aron Hall, DVM, MSPH, Dipl ACVPM	Centers for Disease Control and Prevention
Anita Patel, PharmD, MS	Centers for Disease Control and Prevention
Kathrin Jansen, Ph.D.	Pfizer, Inc.
William C. Gruber, M.D.	Pfizer, Inc.
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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 162nd Meeting of Vaccines and Related Biological Products Advisory Committee meeting. I'm Mike Kawczynski, project manager with FDA, and I will be today's meeting facilitator. This is a live public meeting that is being broadcast in its entirety through C-SPAN, YorkCast, Facebook Live, YouTube, and Twitter.

Today's event is also being recorded and will be posted on FDA's VRBPAC webpage along with all relevant meeting materials. Throughout today's meeting I will be reminding our presenters, committee members, sponsors and OPH speakers as to when they are close to their allotted time and assisting them when needed.

Just a reminder to everyone that once called upon to please manage your mute and activate your webcams. At this time, I'd like to introduce you to Dr. Arnold Monto, the acting chair, who will now provide opening remarks. Dr. Monto, take it away.

DR. ARNOLD MONTO: I'd like to add my welcome to this 162nd meeting of the Vaccine and Related Biological Advisory Committee of the FDA. We have one task ahead of us today, and that is to discuss and vote on the Emergency Use Authorization of the Pfizer BioNTech COVID-19 vaccine for the prevention of COVID-19 in individuals 16 years of age and older. To kick the meeting off, I'd like to call on Dr. Atreya to go through the roll call, introduction of Committee, and administrative statements. As we go around the Committee, I'd like the members to just introduce themselves and their affiliations. So Dr. Atreya, please.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. PRABHAKARA ATREYA: Good morning, everyone. This is Dr. Prabha Atreya, and it is my great pleasure to serve as the Designated Federal

Officer, as our DFO, for today's 162nd Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research and the VRBPAC Committee, I would like to welcome everyone for today's virtual meeting.

Dr. Monto already mentioned the topic for today. Our meeting is Emergency Use Authorization of Pfizer BioNTech COVID-19 vaccine for the prevention of COVID-19 in individuals 16 years of age and older. Today's meeting and the topic were announced in the federal register notice that was published on November 27, 2020. Now, I would like to introduce my excellent staff and also to make a few administrative remarks.

Ms. Kathleen Hayes is my co-designated federal officer providing support today in all aspects of conducting this meeting. Other staff, Ms. Monique Hill, Dr. Jeanette Devine, and Ms. Christina Vert also provided excellent administrative support. Please direct any press or media related questions for today's

meeting to FDA's Office of the Media or fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Alison Bean.

We will begin today's meeting by taking a formal roll call for Committee members and temporary voting members. When it is your turn, please turn on your video camera on and state your first name and last name and your organization. And when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slide in which we will begin with the chair. Dr. Monto, can we start with you, please? Thank you.

DR. ARNOLD MONTO: All right. I'm Arnold Monto. I'm professor of epidemiology in the University of Michigan School of Public Health.

DR. PRABHAKARA ATREYA: Great. Dr. Amanda Cohn? Dr. Cohn, can you unmute your phone?

DR. AMANDA COHN: (Audio distortion).

DR. PRABHAKARA ATREYA: We can't hear you Dr. Cohn.

MR. MICHAEL KAWCZYNSKI: She'll be on shortly. She's reconnecting, so we'll go to the next one.

DR. PRABHAKARA ATREYA: Okay. Dr. Chatterjee?

DR. ARCHANA CHATTERJEE: Good morning. My name is Archana Chatterjee. I'm the dean of the Chicago Medical School and Vice President for Medical Affairs at Rosalind Franklin University of Medicine and Science. I am a pediatric infectious diseases specialist by background.

DR. PRABHAKARA ATREYA: Thank you. Dr. Cody Meissner? Dr. Meissner?

DR. CODY MEISSNER: Thank you. I'm Cody Meissner. I am a professor of pediatrics in the Infectious Disease Division at Tufts University School of Medicine and Tufts Children's Hospital in Boston.

DR. PRABHAKARA ATREYA: Great. Dr. Gans?

DR. HAYLEY GANS: Good morning. This is Dr. Hayley Gans. I'm a professor of pediatrics in pediatric infectious diseases at Stanford University. Great to be here. Thanks.

DR. PRABHAKARA ATREYA: Thanks. Dr. Kurilla, Mike Kurilla?

DR. MICHAEL KURILLA: Good morning. Michael Kurilla, I'm the director of the Division of Clinical Innovations at the National Center for Advancing Translational Science within the National Institute of Health. I'm a pathologist by training, and most of my professional career has been involved in infectious disease drug and vaccine development.

DR. PRABHAKARA ATREYA: Great. Dr. Paul Offit?

DR. PAUL OFFIT: Hi, I'm Paul Offit. I'm a professor of pediatrics in the Division of Infectious Diseases at the Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania.

DR. PRABHAKARA ATREYA: Dr. Annunziato, Paula Annunziato?

DR. PAULA ANNUNZIATO: Good morning. I'm Paula Annunziato. I lead clinical global development

for vaccines at Merck, and I'm here today as the non-voting industry representative.

DR. PRABHAKARA ATREYA: Excellent. Mr. Sheldon Toubman? Mr. Toubman? Okay. Dr. Steve Pergam?

MR. SHELDON TOUBMAN: Good morning. Can you hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can.

DR. PRABHAKARA ATREYA: Yes, thank you.

MR. SHELDON TOUBMAN: Yeah. Good morning. My name is Sheldon Toubman. I'm an attorney. I represent clients mostly in the health area. I'm employed by New Haven Legal Assistance Association, although I'm here today in my personal capacity as a consumer representative.

DR. PRABHAKARA ATREYA: Great. Dr. Steve Pergam?

DR. STEVEN PERGAM: Hi, everyone. I'm Steve Pergam. I'm an associate professor at the University of Washington and Fred Hutchinson Cancer Research

Center, and I focus on infectious diseases.

DR. PRABHAKARA ATREYA: Mike, can we go to the next slide, please? Great. Dr. Fuller, Oveta Fuller?

DR. OVETA FULLER: Good morning. I'm Oveta Fuller. I'm an associate professor of microbiology and immunology at the University of Michigan Medical School and a member of the African Studies Center in the International Institute. And I'm a virologist by training.

DR. PRABHAKARA ATREYA: Great. Dr. Kim, Capt. Kim.

DR. DAVID KIM: Good morning. David Kim, I'm the Director of the Division of Vaccines at the Office of Infectious Disease and HIV/AIDS Policy under the Office of the Assistant Secretary for Health.

DR. PRABHAKARA ATREYA: Great. Dr. Eric Rubin?

DR. ERIC RUBIN: Hi, I'm Eric Rubin. I'm Editor in Chief of the *New England Journal of Medicine*, a professor at the Harvard School -- Harvard T.H. Chan

School of Public Health, and an infectious disease clinician at the Brigham Women's Hospital.

DR. PRABHAKARA ATREYA: Excellent. Dr. James Hildreth?

DR. JAMES HILDRETH: Good morning. I'm James Hildreth. I'm the president and CEO of Meharry Medical College and professor of internal medicine. I'm a viral immunologist by training.

DR. PRABHAKARA ATREYA: Great. Dr. Jeanette Lee?

DR. JEANNETTE LEE: Good morning. I'm Jeanette Lee. I'm a professor of biostatistics at the University of Arkansas for Medical Sciences.

DR. PRABHAKARA ATREYA: Great. Okay. Next slide, please. Dr. Juan Banacloche?

DR. GEA-BANACLOCHE: Good morning. I'm Juan Gea-Banacloche. I'm an infectious diseases clinician at the Mayo Clinic in Phoenix, Arizona.

DR. PRABHAKARA ATREYA: Great. Dr. Mark Sawyer?

DR. MARK SAWYER: Good morning. I'm Mark Sawyer. I'm a professor of pediatrics at the University of California San Diego and Rady Children's Hospital in San Diego, and I'm a pediatric infectious disease specialist.

DR. PRABHAKARA ATREYA: Excellent. Dr. Melinda Wharton?

DR. MELINDA WHARTON: Good morning. I'm Melinda Wharton. I'm an adult infectious disease physician by training, and I'm Director of the Immunization Services Division at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Great. Thank you. Dr. Ofer Levy?

DR. OFER LEVY: Good morning. My name is Ofer Levy. I'm the Director of the Precision Vaccines Program at Boston Children's Hospital and Professor of Pediatrics at Harvard Medical School.

DR. PRABHAKARA ATREYA: Great. Dr. Pamela McInnes?

DR. PAMELA MCINNES: I'm Pamela McInnes, retired deputy director of the National Center for Advancing Translational Sciences at the National Institutes of Health. Good morning.

DR. PRABHAKARA ATREYA: Good morning. Dr. Patrick Moore?

DR. PATRICK MOORE: Good morning. I'm Patrick Moore. I'm at the University of Pittsburgh Cancer Institute and the Department of Microbiology and Molecular Genetics.

DR. PRABHAKARA ATREYA: Great. Dr. Ralph Tripp?

DR. RALPH TRIPP: Good morning. I'm Ralph Tripp from the University of Georgia, and I'm the chair of Vaccine Therapeutics there.

DR. PRABHAKARA ATREYA: Okay. Dr. Stanley Perlman? We can't hear you Dr. Perlman. Mike, can you adjust the volume?

DR. STANLEY PERLMAN: Good morning. I am Dr. Stanley Perlman from the University of Iowa in the

Department of Microbiology and Immunology and in Pediatric Infectious Diseases, and I'm a long-time corona-virologist.

DR. PRABHAKARA ATREYA: Great. I think Dr. Amanda Cohn is available. Can she introduce herself just for a second? We can't hear you.

DR. AMANDA COHN: Can you hear me now?

DR. PRABHAKARA ATREYA: Yes.

DR. AMANDA COHN: Good morning. Sorry for the technical difficulties. I'm Captain Amanda Cohn, Chief Medical Officer at the National Center for Immunization and Respiratory Diseases and a pediatrician by training with an expertise in vaccines in pediatrics.

DR. PRABHAKARA ATREYA: Thank you so much. Okay. Let's now introduce -- the introductions of the FDA staff. First, I would like to introduce Dr. Peter Marks, the head of the Center for Biologics. Dr. Marks?

DR. PETER MARKS: Hi, so thanks very much. It's Peter Marks, Director of Center for Biologics

Evaluation and Research, and I just want to take a moment to thank all of the Committee members as well as everybody who's tuning in right now who might not usually be viewing our usually sedate Vaccines and Related Biological Products Advisory Committee meetings. Thanks very much.

DR. PRABHAKARA ATREYA: Excellent. Let's move on to Dr. Marion Gruber, Director of the Office for Vaccines at CBER.

DR. MARION GRUBER: Yeah. Good morning. My name is Marion Gruber, and I'm the director of the Office of Vaccines Research and Review in the Center for Biologics and Research at FDA. And on behalf of my colleagues in the Office of Vaccines, I also would like to welcome the Committee members, Pfizer BioNTech, as well as the public to today's meeting.

I would like to take the opportunity to thank the members of this Committee for taking time out of their busy schedule to provide their perspectives, their recommendations and advice, regarding the

adequacy of the scientific evidence that will be presented by Pfizer and the FDA today, to support a determination whether the benefits of Pfizer BioNTech's COVID-19 vaccine outweigh its risks to support authorization of this product under an EUA. FDA very much appreciates the Committee's input on this very important topic, and I look forward to today's discussion. Thank you.

DR. PRABHAKARA ATREYA: Great. Thank you, Dr. Gruber. Now, I would like to acknowledge the presence of Dr. Celia Witten, Deputy Director of CBER, and also Dr. Phillip Krause, Deputy Director of Office of Vaccines, who may join later making remarks. So I will now proceed with the Conflict of Interest Statement. Okay.

So the Food and Drug Administration is convening virtually today, December 10, 2020, the 162nd 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 December 10, 2020, the Committee will meet in open session to discuss the emergency use authorization, EUA, of the Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 in individuals 16 years of age and older.

The topic is determined to be a particular matter involving specific parties. With the exception of industry representative member, all standing and temporary voting members for the VRBPAC are appointed special government employees or regular government employees from other agencies, and they're subjected to federal conflicts 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, regular government employees and special

government employee consultants of this committee have been thoroughly 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 18 U.S. Code 208, their employer. These interests may include investments, consulting, expert witness testimony, contracts and grants, Corporate Research and Development Agreements, or CRADAS, teaching, speaking, writing, patents and royalties and primary employment. These may include interests that are current or under negotiation.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict 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's services

outweighs the potential for a conflict of interest created by the financial interests involved or when the interest of the regular government employee is not so substantial as to be deemed likely to affect the integrity of the services with which the government may expect from the employee.

We have the following consultants serving as temporary voting members today. They are Dr. Oveta Fuller, Dr. Juan Gea-Banacloche, Dr. James Hildreth, Captain David Kim, Jeanette Lee, Dr. Ofer Levy, Dr. Pamela McInnes, Patrick Moore, Dr. Stanley Perlman, Eric Rubin, Mark Sawyer, and Ralph Tripp and Melinda Wharton.

Based on today's agenda and all financial interests reported by Committee members and consultants, there has been only one conflict of interest waiver issued under 18 U.S. Code 208 in connection with this meeting. Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's

meeting. The waiver was already posted on FDA's website for public disclosure.

Dr. Paula Annunziato is currently serving as the industry representative to this Committee. Dr. Annunziato is employed by Merck. The industry representatives are not appointed as special government employees and serve as nonvoting members of the Committee. Industry representatives on this Committee is not screened for their financial interests. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the Committee.

Mr. Sheldon Toubman is serving as the consumer representative for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

Today's meeting has multiple external speakers. We have three speakers from the Centers for

Disease Control and Prevention. These are Dr. Nancy Messonnier, Dr. Aron Hall, Dr. Anita Patel. Regular government employees have all been screened for conflicts of interest, and they have been cleared to participate as speakers for today's meeting.

The guest speaker for this meeting is Dr. Steven Goodman, a Professor of medicine and Associate Dean for Clinical and Translational Research at Stanford University. He has been asked to disclose any financial interests he may have related to the product before the meeting. Disclosure of conflicts of interest for guest speakers follow all applicable federal laws, regulations, and FDA guidance.

FDA encourages all meeting participants, including open public hearing speakers to advise the committee of any financial relationships that they may have with any affected firm, its products and, if known, it's direct competitors. We would like to remind standing and temporary members today that if the discussions involve any other products or firms not

already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement, and their exclusion will be noted for 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 to our chair, Dr. Monto. Thank you very much. Dr. Monto?

DR. ARNOLD MONTO: Thank you, Prabha. Here I am. Technical issues, which are going to be one of our biggest problems I predict during the day. Thank you for getting the meeting kicked off. I'd like first -- we're actually running a little early -- to call on Dr. Doran Fink of the FDA to talk about the situation that we are facing and the presentation of a description of the Emergency Use Authorization. Dr. Fink?

FDA PRESENTATION ON EMERGENCY USE AUTHORIZATION

DR. DORAN FINK: Good morning. I'm Doran Fink. I'm the Deputy Director for Clinical Review in the Division of Vaccines and Related Products Applications within the Office of Vaccines Research and Review, Center for Biologics Evaluation and Research at FDA. The VRBPAC last convened on October 22 of this year to discuss the development, licensure, and emergency use authorization of COVID-19 preventative vaccines. Since that meeting, COVID cases and associated hospitalizations and deaths have increased substantially in the U.S. and worldwide.

On November 20, Pfizer submitted an emergency use authorization request for the Pfizer-BioNTech COVID-19 vaccine, otherwise known as BNT162b2. This is an mRNA and lipid nanoparticle vaccine administered as a two-dose regimen 21 days apart. We'll be hearing more about the vaccine and its proposed use in later presentations.

The use being requested for emergency authorization is for active immunization to prevent

COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The information submitted with the request includes safety and efficacy data from a large, randomized, blinded, placebo-controlled phase 3 trial. And these data will be discussed in detail in our afternoon sessions.

Today, we will be considering whether to make available to millions of Americans an as-yet investigational vaccine that has been developed, tested, and reviewed in record time, with additional testing still underway in ongoing studies. The American public demands and deserves a rigorous, comprehensive, and independent review of the data. And that's what FDA physicians and scientists -- all of us career public health servants -- have been doing over days, nights, weekends, and, yes, over the Thanksgiving holiday. This is in addition to months of review work already completed on information previously submitted in preparation for an EUA request.

FDA has been conducting its comprehensive

review of the Pfizer-BioNTech COVID vaccine EUA submission since its submission on November 20. Our review has included verification of clinical data integrity of Pfizer analyses and also our own independent analyses using datasets that were provided in the submission. We have continued an ongoing review of chemistry, manufacturing, and control information, non-clinical data, and review of clinical assays, including information that was submitted shortly prior to the EUA request.

We have been reviewing and revising along with Pfizer, prescribing information and fact sheets for vaccine recipients and healthcare providers. These will be necessary to inform and instruct vaccine recipients and healthcare providers during use of the vaccine under EUA. And these materials are necessarily informed by our review of the data.

We have sent and received back answers to multiple information requests addressed to Pfizer to clarify questions related to the data. And last but

certainly not least, we have been preparing for today's VRBPAC meeting. Today's meeting in which the Committee will advise FDA with its own independent assessment of the data, continues FDA's commitment to an expedited review process that is transparent, scientifically sound and data driven.

The legal authority for Emergency Use Authorization was established in section 564 of the Federal Food, Drug and Cosmetic Act. This legal authority allows for FDA authorization of unapproved medical products, or unapproved uses of approved medical products, to address public health emergencies related to biological, chemical, radiological or nuclear agents. Issuance of an Emergency Use Authorization requires prior determination of a threat, and declaration of circumstances justifying the need for an EUA to address that threat, by the Secretary of Homeland Security, Defense, or Health and Human Services. To that end, Health and Human Services Secretary Azar issued a declaration on March 27 of this

year justifying Emergency Use Authorization of drugs and biological products to address the COVID-19 pandemic.

Once that declaration has been issued, there are four criteria that must be met in order to issue an EUA. First of all, the agent referred to in the EUA declaration can cause a serious or life-threatening disease or condition. We know this to be true for SARS-coronavirus-2 and COVID-19. The second and third criteria are closely linked. There must be a reason to believe that the medical product may be effective to prevent, diagnose or treat the serious or life-threatening condition cause by the agent, and the known and potential benefits of the product should outweigh the known and potential risks of the product.

There are special considerations for a COVID-19 vaccine anticipated for widespread deployment to millions of individuals, and these will be discussed on my next slides. The final criterion is that there should be no adequate approved and available

alternative to the product for diagnosing, preventing, or treating the disease or condition.

At this time, the only FDA approved product for COVID-19 is remdesivir. This is an anti-viral agent that is approved for treatment of COVID-19, not prevention. Additional products have been issued under emergency use authorization but have not been FDA approved. And none of these products is authorized for use to prevent COVID-19. Thus, at this time, there is no adequate approved and available alternative to a COVID-19 vaccine for preventing COVID-19 caused by SARS-coronavirus-2.

In October of this year, FDA released guidance outlining our expectations for submissions requesting emergency use authorization of COVID-19 vaccines, and these expectations were discussed at the VRBPAC meeting in October. There are three main areas covered by our expectation: first, data to demonstrate manufacturing quality and consistency. FDA has reviewed the manufacturing quality and consistency data for the

Pfizer-BioNTech vaccine and found it adequate to support emergency use authorization of the vaccine. This will not be discussed in detail further at this meeting.

Second, we expect clear and compelling safety and efficacy data to support a favorable benefit-risk of the vaccine when rapidly deployed for administration to millions of individuals, including healthy people.

And finally, we expect plans for further evaluation of the vaccine safety and effectiveness, including in ongoing clinical trials, active and passive safety monitoring during their use under EUA as well as observational studies.

In terms of clinical data expected to support an EUA submission for a COVID-19 vaccine, we expect a high bar for efficacy. Efficacy data from at least one well-designed phase 3 trial to demonstrate protection against SARS-CoV-2 infection or disease, with a point estimate of at least 50 percent compared to a placebo. Additionally, the appropriately alpha-adjusted

confidence interval lower bound around that point estimate to be greater than 30 percent. This is to ensure that a widely deployed COVID-19 vaccine will have an appreciable impact.

In terms of safety data, we expect these data from throughout clinical development to evaluate reactogenicity, serious adverse events and adverse events of special interest. And we expect that a high proportion of phase 3 study subjects will have been followed for at least one month after completion of the full vaccination regime.

We have an additional expectation for follow up that I will explain on my next slide. We also expect to be able to review sufficient cases of severe COVID-19 that have occurred in clinical trial participants to assess for signals of enhanced disease and also, if possible, to assess for preliminary evidence of protection against severe disease.

We recognize that a planned, case-driven efficacy analysis, and associated safety analyses at

the same time, could provide data to support an emergency use authorization. We have explained that we expect these analyses to include a median follow up duration of at least two months after completion of the full vaccination regimen. The reasons for that expectation are that, first of all, it allows time for potential immune mediated adverse events to be evaluated, understanding that uncommon but clinically significant immune-mediated adverse events to preventative vaccines generally have onset within the first six weeks following vaccination. A median follow-up of two months also ensures that vaccine efficacy is assessed during the time when adaptive and/or memory immune responses rather than innate responses are mediating protection.

And finally, this follow-up period allows for early assessment of waning protection and for assessment of signals of enhanced disease.

Following issuance of an EUA for a COVID-19 vaccine, we understand and expect that further vaccine

evaluation would be needed for ongoing benefit-risk assessment to support continuation of the EUA. But equally important, further vaccine evaluation would be needed to accrue additional data to support licensure of the vaccine as soon as possible and/or to inform labelling. This further vaccine evaluation following issuance of an EUA would include longer term follow up for safety, including in larger numbers of vaccine recipients and in populations with lower representation than in clinical trials.

Further evaluation would also allow for more precise estimation of vaccine effectiveness, in specific populations, and more robust assessment of effectiveness against specific aspects of SARS-coronavirus-2 infection or disease, for example, asymptomatic infection. This further evaluation would also characterize the duration of protection, could investigate immune biomarkers that might predict protection, and of course would be ongoing monitoring for signals of enhanced disease.

Issuance of an EUA for a COVID-19 vaccine would be contingent upon the ability to conduct further vaccine evaluation, which would occur through a combination of active follow up of vaccine recipients under the EUA, passive monitoring for clinically significant adverse reactions using established reporting mechanisms -- for example, the vaccine adverse events reporting system -- observational studies including those that leverage healthcare claims databases and, finally, continuation of blinded placebo-controlled follow up in ongoing clinical trials for as long as is feasible, and strategies to handle loss of follow ups in those trials.

We acknowledge that placebo-controlled blinded follow up cannot continue indefinitely as more information about a vaccine's safety and effectiveness becomes available. However, FDA does not consider issuance of an EUA for a COVID-19 vaccine to necessitate immediate unblinding of ongoing clinical trials or offering vaccine to all placebo recipients.

Of course, trial participants may choose to withdraw from follow up for any reason, including to receive vaccine made available under EUA. And it may be possible to offer vaccine to placebo recipients in clinical trials in a reasonable timeframe that doesn't compromise the integrity of the clinical trial. And these considerations will be discussed further this morning.

When an EUA is issued for a COVID-19 vaccine, it will specify conditions of use for which benefit-risk has been determined to be favorable based on review of the totality of available data, including those populations to be included or excluded from the EUA, conditions for vaccine distribution and administration and requirements for safety monitoring and reporting of adverse events. Vaccine made available under an EUA will also include provision of information to vaccine recipients and healthcare providers via prescribing information and fact sheets. These materials will describe that the product remains

investigational, will inform about the known and potential benefits and risks, and will also make clear what are the available alternatives, and the option to refuse vaccination.

Once issued, an EUA may be revised or revoked for a number of reasons: first of all, if circumstances justifying the EUA no longer exist; second, if criteria for issuance are no longer met; and third, or any other circumstances that arise that warrant changes necessary to protect public health or safety. These other circumstances may be based on new information concerning vaccine safety or effectiveness, vaccine manufacturing or quality, or COVID-19 epidemiology or pathogenesis.

The agenda for today's VRBPAC meeting will include, following the conclusion of my talk, first, three presentations from the CDC providing an update on COVID-19 epidemiology, plans for vaccine safety and effectiveness monitoring under an EUA and operational distribution plans for the vaccine under an EUA. We

will then hear about considerations for placebo-controlled trial design if an unlicensed vaccine becomes available. Following lunch, we will have an open public hearing and then we'll dive into a discussion of the data; first with a presentation by Pfizer and then an FDA presentation.

At the end of the day, we will have a Committee discussion and a vote. We have two questions that we would like the Committee to consider for discussion. These will not be voting questions. First, Pfizer has proposed a plan for continuation of blinded placebo-controlled follow up in ongoing trials if the vaccine were made available under EUA. We would like the Committee to discuss Pfizer's plan, including how loss of blinded placebo-controlled follow-up in ongoing trials should be addressed. Second, we would like the Committee to discuss any gaps in plans described today, and in the briefing documents, for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech vaccine

under an EUA.

Following discussion of these items, we will have a single question for the Committee to vote on. The question is: based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 vaccine outweigh its risks for use in individuals 16 years of age and older. This concludes my presentation. Thank you very much.

DR. ARNOLD MONTO: Thank you, Dr. Fink, for a very clear presentation. We have a fair amount of time before the next scheduled presentation, which is very good because I think there are some questions of clarification that the committee may have about our guidelines for discussion and for our eventual vote.

So committee members, please raise your hands if you would like to ask Dr. Fink some specific questions. We don't want to start our discussion of the points raised by Dr. Fink, but just clarification about the characteristics of an Emergency Use Authorization and the other guidelines. So please

raise your hand. I may be having some technical difficulties, so Mike, you may need to --

MR. MICHAEL KAWCZYNSKI: Yeah. I got it.

DR. ARNOLD MONTO: -- recognize the person. Go ahead.

MR. MICHAEL KAWCZYNSKI: No problem. All right. The first one we have is Dr. Sawyer. Would you go ahead and turn your camera on?

DR. MARK SAWYER: Thanks very much, Dr. Fink. You mentioned that issues related to manufacturing can be one of the reasons to revise or revoke an EUA. What is the monitoring process going forward, from this point, with regard to manufacturing process?

DR. DORAN FINK: Thank you. So FDA continues to engage with the vaccine manufacturer concerning manufacturing quality and control issues to ensure that these remain adequate to support use of the vaccine under EUA. I'll invite any of my other FDA colleagues to comment further.

DR. MARION GRUBER: Yeah. This is Marion.

Can you hear me, Mr. Chairman?

MR. MICHAEL KAWCZYNSKI: Yes, we can. We can hear you.

DR. MARION GRUBER: Okay. Thank you very much. So I think I wanted to second what Doran just said. It is true that the monitoring of the CMC -- that is the Chemistry Manufacturing and Control information -- that is currently available, and we, of course, will get additional data from the different manufacturing sites. We will review most of this information, and we will work together with the vaccine manufacturer to make sure that the product that is made and generate is of adequate consistency and quality. So this is work that's going to be ongoing over the next month.

DR. MARK SAWYER: Thanks very much.

MR. MICHAEL KAWCZYNSKI: Okay. Arnold, are you able to see the list?

DR. ARNOLD MONTO: No, that side of my screen I see, but there's no activity there.

MR. MICHAEL KAWCZYNSKI: Okay. That's all right.

DR. ARNOLD MONTO: Why don't you manage the calling on?

MR. MICHAEL KAWCZYNSKI: We'll take care of that. Dr. Kurilla?

DR. MICHAEL KURILLA: Thank you. I don't know why my camera's not working, but it says it's on. Doran, just trying to understand the question we're being asked to vote on is what Pfizer has requested. But if I understood your talk correctly, the FDA can limit the actual -- can place limits on the target populations through the specific indications regarding the EUA. My question is, how do you view the investigational status of the product under an EUA?

DR. DORAN FINK: Thank you for the question. So a product that is made available under an EUA is an unapproved product. It has not been FDA licensed.

DR. MICHAEL KURILLA: If I can just follow up with that. So, if you limited the EUA to a specific

set of populations, even those populations that have the EUA, placebo-controlled trials would still be possible from that perspective?

DR. DORAN FINK: Well, we will have a discussion on those considerations later this morning. But in FDA's view, issuance of an EUA for a COVID-19 vaccine should not preclude the conduct of placebo-controlled trials. In particular, in situations where that vaccine made available under an EUA is available only in limited quantity.

DR. ARNOLD MONTO: Okay. I think I can see now. Thank you for fixing it. Dr. Lee?

DR. JEANNETTE LEE: So thank you. One of the questions I have is a little bit more general. I recognize we're considering the Pfizer product for an EUA today. However, future EUA applications, if, for example, there is a vaccine that is approved under a BLA -- vaccine number one, let's just call it that -- will that make it more challenging for future products to request an EUA?

DR. DORAN FINK: Right. I think what you're getting at is the fourth criterion for issuance of an EUA, which says that there must not be any adequate approved and available alternative therapy.

DR. JEANNETTE LEE: Yes. Correct.

DR. DORAN FINK: So first of all, if a vaccine is made available under an EUA, it is not approved, and so therefore that would not preclude issuance of an EUA for another vaccine. If a vaccine is approved by FDA, that would also not necessarily preclude issuance of an EUA for another investigational COVID-19 vaccine.

For example, if the approved vaccine is available only in limited quantity, then it may not be considered adequate to address the public health emergency. Second of all, if the vaccine that is approved is approved for use only in a limited population, then that vaccine may not be considered adequate to address the needs of the public health emergency for other populations.

DR. JEANNETTE LEE: Thank you.

DR. ARNOLD MONTO: Mr. Toubman?

MR. SHELDON TOUBMAN: First of all, thank you. Wonderful job.

DR. ARNOLD MONTO: Can you speak a little louder, please? We're having problems hearing you.

MR. SHELDON TOUBMAN: Oh, yes. Sorry. Just thanking Dr. Fink and everybody at the FDA for all the work they've done independently reviewing the data. Thank you. Two questions, one is you indicated that since the submission came in from Pfizer you've had a lot of ongoing discussions with them. And the first question is does that include getting updated data? Because the closing dates of data that's in their submission is November 14, which is 26 days ago, which is almost a month. It's about half of the entire period for the two months minimum required for EUA. So have you gotten more recent requests -- gotten more recent data?

And the second question is a follow up to Dr. Kurilla's. The question is, you've given us only one

question, and that is yes or no to recommending approval for the entire amount, which is population, which Pfizer's requesting which is the entire 16 and over. But certainly the committee could view this as something they'd like to grant EUA for, but given the balancing of risk and benefit, it may be different for different populations. So we might want to grant it or recommend it for a smaller set than Pfizer's asking for.

But your question doesn't seem to allow for that. And I was wondering if you have a backup question that might be used. I know that in the past with the dengue review -- just a backup question. Just ask if you could answer this.

DR. ARNOLD MONTO: Okay. So could I say that your last question, we can bring that up during the discussion later on. So I'm going to excuse Dr. Fink from having to answer that part of the question.

DR. DORAN FINK: Thank you. To answer your first question, no, we have not received additional

datasets beyond the datasets that were submitted to us comprising a cutoff date of November 14. As you can imagine, there is tremendous amount of work that goes into preparing a dataset for submissions, and so it really is infeasible for the sponsor and for FDA to be chasing our tails trying to get datasets that encompass more and more data as time goes on. That being said, if the sponsor becomes aware of, or if we become aware of, any data that would potentially impact our benefit-risk assessment, we do have discussions with the sponsor regarding those data.

DR. ARNOLD MONTO: And we will be able, Mr. Toubman, to ask questions of the sponsor after their presentation later on. So we can revisit this issue. Next, Dr. Perlman.

DR. STANLEY PERLMAN: So I just had a question about the last part of what you were talking about when you talked about how Pfizer was going to deal with the issue of placebos going off the vaccine trial. And you asked for advice from the committee. Is that part of

the EUA vote, or is that a separate issue?

DR. DORAN FINK: No, that is not a question for a vote. It's just an item for discussion. We'd like to hear the committee's thoughts on the plan that is being proposed by Pfizer, which you will hear about in greater detail later today.

DR. ARNOLD MONTO: Dr. McInnes?

DR. PAMELA MCINNES: I have a question that's sort of a follow up from Mike Kurilla originally started. Given that this is considered an investigational product under an EUA, I'm assuming that any manufacturer cannot actually market such an investigational vaccine. Is that correct?

DR. DORAN FINK: So Emergency Use Authorization does not allow for commercial distribution of the vaccine via the usual marketing that would be available to a licensed vaccine. I hope that clarifies things. If anyone else from FDA wants to chime in, I'd welcome the additional remarks.

DR. PAMELA MCINNES: So Doran, thank you. I'm

happy to get the comments. I'm just trying to understand. So it's not marketed traditionally, but compensation for an investigational vaccine is possible under an EUA, like for a government entity?

DR. DORAN FINK: So again, this is not my area of expertise.

DR. PAMELA MCINNES: I understand.

DR. DORAN FINK: The Emergency Use Authorization may include conditions related to advertising and other similar issues. In terms of transfer of money between vaccine recipients and providers, or between the U.S. government and the manufacturer, I can't speak to those.

DR. ARNOLD MONTO: Dr. Meissner?

DR. CODY MEISSNER: Thank you, Dr. Monto, and I would like to thank Dr. Marks and Dr. Fink and Dr. Gruber, and everyone else at the FDA, because the amount of work that you have done is just extraordinary. And the briefing packets that have been circulated are clear and extremely helpful, so thank

you very much for your ongoing work.

The question I have for you is it will be advantageous, for a number of reasons, to have one of the COVID-19 vaccines available under a biologic license application instead of an EUA. And I realize it's a difficult question, but can you offer any comments about the route or the pathway forward for the FDA to begin to think about when you've reached a point that you would consider a BLA?

DR. DORAN FINK: Yes. So first of all, we do want any vaccine that is made available under an EUA to continue its testing to allow for its licensure as soon as possible after issuance of the EUA. So this continued evaluation, as I explained in my presentation, I think first and foremost would include some longer term follow up of participants enrolled in ongoing studies, as well as safety and effectiveness data coming out of use of the vaccine under the EUA.

This additional evaluation would then meet our usual expectations for clinical data to be included in

a licensure application. There are some other sources of information that involve manufacturing and facilities, and potentially nonclinical studies as well, that we would typically require to support a licensure application but are not absolutely necessary to support issuance of an EUA.

DR. CODY MEISSNER: Is it possible to predict or estimate when conditions of safety and efficacy might be satisfied for BLA?

DR. DORAN FINK: In terms of the time it would take? Yeah. I couldn't predict, but I will say that we typically ask for at least six months of follow up in a substantial number of clinical trial participants to constitute a safety database that would support licensure.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: And finally, Dr. Fuller?

DR. OVETA FULLER: My question -- did I understand you to say that the FDA in the October 22 meeting looked at the manufacturing quality of the

Pfizer vaccine and that was satisfactory? And if so, how will that be valuated in the actual distribution of the vaccine, and will we talk about that later?

DR. DORAN FINK: Right. So to clarify what I said earlier, as part of the EUA submission and in information submitted prior to the EUA, FDA's been conducting an ongoing review of manufacturing quality, consistency, and control. And we have found this information to be adequate to support emergency use authorization of the vaccine.

We are not intending to discuss details of the manufacturing process, many of which are proprietary, during today's meeting. But as Dr. Gruber and I discussed in response to a previous question, our review of the manufacturing information is an ongoing process and will continue even after the vaccine is authorized, if that is the decision that we make.

DR. OVETA FULLER: Okay. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Fink. You've kicked us off with a lot of information, which

we're going to be coming back to later on this afternoon. I'd like next to call on Dr. Aron Hall from CDC who's the co-lead in the epidemiology taskforce, and he is going to give us an update about the current situation.

UPDATE ON EPIDEMIOLOGY

DR. ARON HALL: All right. Thank you very much. Good morning. Can you hear me okay?

DR. ARNOLD MONTO: Yes, we can.

DR. ARON HALL: Wonderful. So good morning. I'm Dr. Aron Hall, co-lead of the epidemiology taskforce in CDC's COVID-19 response and chief of the Respiratory Viruses Branch. To help further subsequent discussions today about COVID-19 vaccines, I would like to provide a brief update on the current epidemiology of COVID-19 in the United States. As of December 8, over 4.8 million COVID-19 cases and over 280,000 associated deaths have been reported in the United

States.

The initial peak in early April was driven largely by elevated activity in the New York Metro area, followed by a second larger peak, in late July, primarily due to increase activity across much of the southern U.S. Since mid-September, daily counts of new cases have again been on the rise, with even sharper increases since mid-October. Since submission of these slides in advance of this meeting, we have now surpassed 15 million cases and 285,000 deaths nationally, with over 200,000 new cases and over 2,500 new deaths reported yesterday.

In addition to reported cases, CDC uses several other systems to track the pandemic, which are compiled in the weekly surveillance summary called COVIDView. This weekly report includes the percent positivity of molecular tests for SARS-CoV-2, the virus that causes COVID-19, shown in blue, as well as syndromic surveillance for COVID-19-like illness, or CLI, among ambulatory patients, shown in red.

Both of these leading indicators have been increasing since September. Also included in COVIDView are weekly hospitalization rates, shown in grey, which are currently at the highest point since the beginning of the pandemic. And also the percent of deaths due to COVID-19, influenza, or pneumonia based on death certificates, shown in green, both of which are lagging indicators that have been increasing since October.

One component of the weekly COVIDView report is an assessment of COVID-19 hospitalizations through COVID-NET. COVID-NET conducts hospitalization surveillance in 14 states, representing about 10 percent of the U.S. population. Patients must be a resident of the surveillance area and have a positive SARS-CoV-2 test within 14 days prior to or during hospitalization. Medical chart reviews are conducted by trained surveillance officers and data are updated weekly on an interactive website.

While focused on the more severe end of the illness spectrum, COVID-NET provides active population-

based surveillance, thus overcoming some of the biases with passive surveillance and providing robust data on the epidemiology of COVID-19. Looking at weekly hospitalization rates by age, we see that each of the peaks in April, late July and currently have been most pronounced among adults age 65 years and older. Hospitalization rates in children have been considerably lower than those among adults but have remained stable or increasing since the spring. Note that the last few data points are subject to reporting lag and may increase subsequently.

Looking at the cumulative hospitalization rates through late November from COVID-NET and stratifying by age group, we see a strong increasing trend with increasing age. As of November 28, adults age 65 years and older had a cumulative rate of 756 per 100,000, which is roughly equivalent to one in every 130 people in this age group being hospitalized with COVID-19. This rate is approximately four and a half times greater than that of adults age 18 to 49.

COVID-NET surveillance has also helped to identify significant racial and ethnic disparities in the rates of COVID-19. Shown here are age-adjusted cumulative hospitalization rates by race and ethnicity. Demonstrating rates are three to four times greater among persons that are Hispanic or Latino, non-Hispanic American Indian or Alaska Native, or non-Hispanic Black or African-American, compared with those that are non-Hispanic white. These disparities are likely multifactorial, potentially influenced by differential exposure rates, prevalence of underlying medical conditions, access to care, and other socioeconomic factors.

To help further tease apart these issues and identify risk factors for severe COVID-19, CDC and public health partners analyzed the relative rates of in-hospital mortality from COVID-NET using models that adjust for age, sex, race, and ethnicity, smoking and several underlying medical conditions. As shown in the red box, older age was the strongest independent risk

factor for in-hospital death, and the risk increased with increasing age. Other characteristics significantly associated with in-hospital mortality include male sex, immunosuppression, renal disease, chronic lung disease, cardiovascular disease, neurologic disorder, and diabetes.

Combining data with COVID-NET with population-based data from the Behavioral Risk Factor Surveillance System, or BRFSS, we likewise developed models to assess risk for COVID-19 hospitalization among adults with specific underlying conditions. Again, after adjusting for age, sex, and race and ethnicity, the risks for COVID-19 associated hospitalization was greatest for adults with severe obesity, chronic kidney disease and diabetes, as shown in the red box. Compared with adults without these conditions, those that have them were three to five times more likely to be hospitalized for COVID-19.

Furthermore, the risk of COVID-19 hospitalization increased with the number of underlying

medical conditions, as shown in the red box on this table. While specific risks varied depending on the specific underlying medical condition, adults with three or more conditions had five times the risk of COVID-19 hospitalization compared to adults with no conditions. Due to increased age, underlying medical conditions, and their congregate living situation, residents of long-term care facilities have been disproportionately impacted by COVID-19.

As shown here, residents of these facilities comprise nearly 50 percent of COVID-19 hospitalizations among adults age 75 to 84 years, and nearly two-thirds of COVID-19 hospitalizations among adults age 85 years and older. As such, the Advisory Committee for Immunization Practices, or ACIP, recently recommended long-term care facility residents as a priority group to receive initial doses of COVID-19 vaccines once approved. Similarly, healthcare personnel have been prioritized for vaccination to preserve capacity to care for patients with COVID-19 and other illnesses.

Again, based on COVID-NET data, 6 percent of adults hospitalized with COVID-19 were healthcare personnel, with nursing related occupations being the most frequent. Healthcare personnel hospitalized with COVID-19 had similar prevalence of underlying medical conditions, most notably obesity, as that observed among adults hospitalized with COVID-19 -- all adults. Likewise, a similar proportion of severe clinical outcomes, including ICU admission, mechanical ventilation, and death, occurred among healthcare personnel as that across all adult COVID-19 hospitalizations.

As we prepare for COVID-19 vaccines, it's important to establish baselines to assess their future impact and maintain ongoing assessment of the total burden of SARS-CoV-2 infections in the U.S. To that end, CDC has implemented a nationwide seroprevalence survey to help track the number of people with evidence of previous SARS-CoV-2 infection, including milder infections that do not result in care seeking or

testing for acute infection. These involve biweekly testing of approximately 50,000 residual specimens from commercial laboratories for antibodies against SARS-CoV-2.

Through the first few rounds of this survey, estimated seroprevalence has ranged from 0.4 to 23 percent across U.S. jurisdictions. However, as of late September, less than 10 percent of specimens from most jurisdictions had evidence of previous SARS-CoV-2 infection. In general, the highest seroprevalence was observed among children and adults aged less than 50 years, and lowest among older adults age 65 and older.

Using a different multiplier modelling approach, which uses reported cases and other data sources to then account for under detection and under reporting, CDC recently released estimates of the total number of hospitalizations, illnesses, and infections with SARS-CoV-2 in the U.S. This analysis estimated that one of every 2.5 hospitalized cases, and one of every 7.1 non-hospitalized cases, may have been

nationally reported.

Applying these multipliers to reported cases through the end of September yielded a national estimate of 2.4 million hospitalizations, 44.8 million illnesses, and 52.9 million total infections. As the figure to the right shows, most estimated hospitalizations occurred among older adults, while most illnesses and infections were among younger adults.

So in summary, now, as of December 9, over 15 million cases and over 285,000 deaths associated with COVID-19 have been reported in the United States. However, based on seroprevalence surveys and models, the total estimated number of infections is likely two to seven times greater than reported cases. Though, less than 10 percent of the population in most states had evidence of previous infection through September.

Factors associated with increased risk for severe COVID-19 included older age, racial and ethnic minority group membership, and several specific

underlying medical conditions. Ongoing surveillance and epidemiologic studies will help inform further development and implementation of candidate vaccines, including assessment of their impacts, safety, and effectiveness.

Lastly, even with the promising advent of COVID-19 vaccines, there's continued need for non-pharmaceutical interventions, including mask use, physical distancing, hand hygiene, and environmental disinfection to help bring an end to this devastating pandemic. Finally, I would like to acknowledge the thousands of public health professionals that have worked tirelessly over the last 11 months on the CDC COVID-19 response, including the dedicated staff from the Respiratory Viruses Branch. Thank you.

DR. ARNOLD MONTO: I think I wasn't on at first. Thank you so much for being clear about the differential impact of COVID-19 in the U.S. population. We have time for relatively few questions. I see, Dr. Meissner, you have your hand raised.

DR. CODY MEISSNER: Yes, sir. Thank you very much for that presentation, doctor. I would like to ask you about the severity of disease particularly in older adolescents, that is individuals who are 16 and 17 years of age, because they have been included in the company's request for an EUA. I assume it's unlikely that hospitalizations and disease are broken down by age, but is it safe to assume that adolescents who are 16 and 17 years of age are similar in the five- through 17-year-old age group?

DR. ARON HALL: Yeah. Thank you for that question. So of course as we refine to smaller and smaller age brackets, the numbers get smaller, particularly in children where overall we see lower rates, particularly of severe disease -- of hospitalization. In general, we do see higher rates of hospitalization among children aged zero to five relative to those age five to 17. Of course, this is potentially confounded by differential rates of care seeking.

As you might imagine, there are certainly lower thresholds for care seeking for the very youngest and most vulnerable children. However, as we start to look at the more mild end of the illness spectrum and look at rates of detection of SARS-CoV-2 virus using molecular assays, we do see indication of higher rates of infection among older children, among adolescents, particularly, then, as we move into kind of older teenagers and people in their young 20s. Much of this may have been driven in part by outbreaks in the fall among institutes of higher education.

But the broader impacts in children perhaps are not entirely clear until the full resumption of normal activities ensues in the United States, including in person education across all schools in the United States. So we'll continue to monitor closely, but thus far the indication is the highest rates of severe illness in young children but higher rates of infection in older children.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Dr. Rubin?

DR. ERIC RUBIN: Thanks, Dr. Hall. I was interested in the multiplier that you described that applies to the diagnosis of infection. Do you think that applies to deaths as well?

DR. ARON HALL: Yeah. So we have used, at CDC, the same multiplier model previously for tracking influenza and generating in-season estimates of the disease burden. And that same approach has been used previously to estimate deaths in the same manner that are presented today for hospitalizations and milder illness. There're, of course, differential multipliers that would have to be considered for deaths as the rates of underreporting of death are different than those for milder infection.

In general, we have better capture of deaths. We have lower rates of underreporting and under-ascertainment for deaths. But as folks are aware, the dynamics of the pandemic itself have greatly changed those multipliers, and so there's also a considerable

time component that needs to be factored in when using these multiplier models. So the underreporting of deaths, for example, has changed over time, and the attribution of deaths to COVID-19 has changed overtime, which complicates interpretation. But we do have several efforts underway using these models and other approaches to generate estimates of death. And we do feel, as with hospitalizations and illnesses, that the reported number of deaths is likely an underestimate of the true number of deaths.

DR. ERIC RUBIN: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gans, we're going to go over a little bit. Please keep your question short.

DR. HAYLEY GANS: Thank you very much. Thank you for that, and I agree, heroic effort to all of the people who are working on this. I had two quick questions. The data concerning the immunocompromised or immunosuppressed individuals is not really granular enough to make it something that we can use in terms of

how we're thinking about high-risk populations. There are registries looking at this, but it would be nice if there was some national information that you could provide to us. As well as I didn't see any information from pregnant women, which is a population which we're all concerned about. And which we've definitely seen post-natal transmission to very young infants who end up being hospitalized. So if you would just take those up.

DR. ARON HALL: Yeah. Thank you for those comments. Absolutely, there are numerous surveillance efforts currently underway to assess the impacts of COVID-19 in pregnant women. In the interest of time, unfortunately, today I didn't have a chance to present those. But through COVID-NET, as described today, as well as another surveillance system called SET-NET, which was established during the zika epidemic, we have been very closely monitoring the impacts of COVID-19 in both pregnant women and subsequently following up with their infants.

Thankfully, the rates overall have been relatively low thus far. But as we continue to accumulate a critical mass of data in this demographic, we indeed do hope to have more specific estimates of the risks that are imposed to pregnant women and their infants. The early indication is that there may be a higher risk of pre-term delivery among pregnant women infected with COVID-19 relative to women without COVID-19. But there's ongoing efforts to assess those and other potential pregnancy-related risks and fetal outcomes.

DR. ARNOLD MONTO: Thank you very much, Dr. Hall, and it's now time for our morning break. We've eaten into the time a little bit, but I do want to start again at 10:30 Eastern so we can hear from Dr. Messonnier from CDC. See you later.

[BREAK]

MR. MICHAEL KAWCZYNSKI: All right. Welcome

back from break. We'll now enter our second half of our next group of speakers. Arnold?

DR. ARNOLD MONTO: We're next going to hear from -- again from the Centers for Disease Control. We're going to have a few presentations and questions afterwards. First, we're going to hear a presentation from Dr. Nancy Messonnier, the Director of the Center for Immunization and Respiratory Diseases, on vaccine safety and effectiveness monitoring, and then from Anita Patel, the Deputy of the Vaccine Task Force on operational distribution plans. Dr. Messonnier?

VACCINE SAFETY AND EFFECTIVENESS MONITORING

DR. NANCY MESSONNIER: Thank you, Dr. Monto, and thank you for the opportunity to speak today on this really auspicious day. Despite the completely appropriate size and scope of the clinical trials, it's always important to continue to monitor vaccines post-licensure or post-authorization. And that is certainly

especially true with COVID vaccines.

I'm going to talk about the U.S. government plans for monitoring of safety and effectiveness. First, safety. The rapid implementation of safety monitoring under an EUA requires a whole of U.S. government approach with an initial focus on the early populations targeted for vaccination, voluntary active surveillance of adverse events focused on healthcare worker vaccination, and rapid follow-up of reported serious adverse events. As the program continues and more vaccine is given, active surveillance systems will provide increasingly useful information on safety in different populations. Close collaboration of safety experts across the USG will facilitate data sharing and rapid recognition of responses to safety signals.

Now, there is a quite extensive plan for safety monitoring, but I'm just going to summarize a few high points. On day one of the COVID-19 vaccine programs, systems will be in place to monitor the safety of vaccine recipients. These include the

traditional systems that we use -- VAERS, which is the national spontaneous reporting system monitored and implemented by CDC and FDA, but also similar programs at DOD and the VA as well as the National Healthcare Safety Network, or NHSN, which is an acute care and long-term care facility monitoring system. CDC's CISA system is stood up, that provides individual case consultation.

But in addition to really enhance this period, CDC has stood up a new system called V-safe. It's an active surveillance tool that uses text messaging and web-based surveys to monitor vaccine recipients for adverse events. Recipients complete brief surveys up to intermittent surveys to 12 months following vaccination. But then as part of the program, recipients that report a significant health event that impacts their daily activities, or leads them to seek medical attention, will be called for more information and a report will be generated. This is an opt-in system, so we're going to have heavily enhanced

engagement around implementation of the program. We really need people to sign on to this system to give us the best data possible.

Large, linked database monitoring systems will provide safety data when vaccine becomes more widely available in the priority groups and the general public. This includes, again, existing systems like VSD, the FDA's extensive system, and systems from DOD and VA. We're enhancing this by Genesis, which is a new collaboration with NIH and Brown University, to monitor safety in long-term care facility residents. This system operates nationally and has near real time data for 250 facilities.

To look at this another way, this is a table that showcases the systems that we'll be using to monitor safety in the populations that, based on ACIP recommendations, will be vaccinated first, specifically healthcare workers and long-term care facility residents. So you'll see that early on we have a series of systems to monitor healthcare workers and

long-term care facility residents through VAERS. VAERS will be enhanced in this time period, especially around long-term care facility residents, to ensure that we're getting those reports. And then V-safe which will specifically target healthcare workers.

And then you'll see all the systems that are going to be in place for later monitoring in all of those populations. I think the team has done a really good job of thinking through what systems we have, how to enhance those systems and looking for any weaknesses and attempting to fill them in. And I'm giving it short shrift by going through it so quickly, but hopefully you'll understand how robust these systems are.

In addition, the ACIP COVID Vaccine Safety Technical Sub-Group was established to provide expert consultation on COVID-19 vaccine safety issues. This group, which we call VaST, was built off lessons learned during H1N1 safety monitoring. The terms of reference and composition have been finalized, and VaST

is ready to begin reviewing data once implementation commences. The group is co-chaired by a member of ACIP and a member of the National Vaccine Advisory Committee or NVAC. There are 10 independent expert consultants that make up the group, as well as ex officio members from NIH, FDA, OIDP, CMS, HRSA, and IHS. And we also have representatives from the VA and the DOD.

Now to briefly summarize our efforts around post-authorization vaccine effectiveness. Post-authorization or post-licensure VE estimates are needed to address important evidence gaps from phase 3 clinical trials, particularly for secondary endpoints that may not be adequately addressed. For example, the trials may be limited in their ability to address a VE against secondary endpoints like infection transmission or in subpopulations. And we won't have great data early on the duration of protection. We also believe it's important to evaluate the real-world performance of vaccines as protection may differ from efficacy under trial conditions.

So this table attempts to lay out the VE policy priorities that were determined based on consultants with policy experts and internal and external experts. The most immediate priority is to determine whether the vaccine protects against symptomatic disease as expected based on the phase 3 trial data but understanding that implementation for these vaccines might be slightly complicated by folks who don't exactly get the second dose exactly on schedule ,and by the necessity to keep the vaccine in cold chain. So that's going to be the focus, but then there are a variety of subsequent and late stage studies that are being planned or implemented.

A number of strategies are used to plan for the assessment of VE, but to facilitate a rapid launch, we've leveraged existing platforms. And for early-stage vaccination, we focused on populations likely to be vaccinated first. We're harmonizing and coordinating across the U.S. government on a variety of platforms, for example, using common case definitions,

data elements, and methods to improve comparability of results. And we've been working to combine similar platforms to improve geographic representation, increase statistical power and generate more timely and robust VE estimates. And we do have a diversity of methods as we understand that all observation methods have limitations.

Here's a summary of the studies that are being planned, and, again, I don't have time to go through all of them. But I would just point you to the top row. The most immediate question is whether vaccines work as expected. We're planning a prospective study among healthcare workers. There is no large existing databased rich for this group, and so we're doing a test negative design case control study among healthcare workers, which should help us relatively quickly assess this outcome.

So in summary, planned VE studies will provide a robust assessment of COVID-19 vaccine performance in real-world settings. We believe we will have early VE

estimates in groups prioritized for vaccination, VE against key outcomes and in important sub-groups, and data from these studies will address critical gaps and help guide future use of vaccine.

Systems are in place to monitor the safety of COVID-19 vaccination in healthcare workers and long-term care facility residents. V-safe, VAERS, and NHSN will detect adverse event signals for further follow up and evaluation. CMS, Genesis, and other claims based and EHR systems will be used for both signal detection and evaluation. Vaccine effectiveness in healthcare workers is the immediate priority and will address the question of does the vaccine work as expected? We expect those studies to start immediately.

Vaccine effectiveness evaluations in older adults, including those in long-term care facilities, are planned and include both test negative design and cohort evaluations. I hope that that does justice to all the systems that we're planning and that are in place. Understand that vaccine safety and effective

monitoring is a top priority for the U.S. government. And we're committed to ensuring that all these systems are in place and ready to go as soon as the vaccine program is implemented. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Messonnier. We're going to go directly on to Dr. Patel's presentation, and then we'll have questions afterwards so we have plenty of time. Dr. Patel?

OPERATIONAL DISTRIBUTION PLANS

DR. ANITA PATEL: Great. Thank you so much. So thank you for having me today, and we'll be walking through today at a high level what the USG's distribution strategy is for a COVID vaccine, specifically focusing around this Pfizer vaccine product. The USG plan for COVID vaccine distribution will adjust as volume of vaccine doses increases. Early on, we do anticipate that we'll have a constrained supply where vaccine administration is

really targeted towards select population groups, and distribution will facilitate that. As sufficient supply becomes available and the populations that we're trying to reach expand, our distribution network will also further expand.

This schematic here outlines what our concept is for distribution at a very high level. All vaccines will be ordered through CDC's COVID vaccine ordering systems. For the Pfizer vaccine, we will be providing those vaccine orders directly to the manufacturer for distribution to administration sites. We've been working very closely with our state and local partners to make sure that they have plans in place to identify providers that are able to receive, store, and use the vaccine for the specific populations that they're trying to reach. These administration sites will be receiving the Pfizer vaccine product, and they should expand, as well, over time as the targeted populations we're trying to reach expand.

In addition to the hospitals, the vaccination

clinics that have been set up to support early distribution and use of Pfizer vaccine, we have also set up a program called the Long-Term Care Facility Pharmacy Program. This federal program is a partnership that allows for jurisdictions to be able to opt-in to the program, allowing for onsite vaccination support to occur to long-term care facilities. Our pharmacy partners would be providing the onsite vaccination support for those facilities that actually sign up for the program.

I'd also like to draw your attention to the Operation Warp-Speed Coordination cell at the bottom of this slide. The idea is for us to be able to have a clear understanding of what is happening in terms of supply of vaccine as well as administration and uptake information throughout the vaccination program.

Focusing a little bit more on the long-term care facility plan, in order for us to be able to reach skilled nursing facilities we have been working to bring skilled nursing facilities on board to the

program and opt-in. Once a state determines that they're ready to expand vaccination to reach staff and residents within skilled nursing facilities and other assisted living facilities, the program would be turned on. Right now, we do have a very high percentage of the skilled nursing facilities within the United States that have opted in to receive services from the federal program.

The vaccine characteristics of the Pfizer program have actually -- are very different and unique compared to other vaccines that we've seen before, and they do impact distribution, site storage, as well as administration requirements. The details depicted on this slide are very specific to the Pfizer program and outline some of the challenging requirements of the vaccine that have to be implemented in terms of vaccine distribution and storage sites. The additional planning that is needed for distribution, storage, handling, and use has been underway for the last few months based on the information we know for the Pfizer

products.

There is a dedicate cold chain given that the products have to be managed at ultra-low temperature requirements. In addition, the timing of the vaccine, ancillary supplies, which include the diluents, as well as dry ice replenishment has also been a challenge. We have built the distribution system in a way that all three of these elements will arrive within a 36-hour period of time. So once the vaccine is there, these additional pieces will also be delivered to the vaccination site.

Another major challenge that we've had with the product is the actual minimal order requirement. 975 doses is the smallest volume of product that can be ordered for the Pfizer vaccine. This has posed challenges especially in rural areas of the country where that volume of product is more difficult to manage. And it's also been a planning factor that, at the local level, has been used to determine where exactly the product should be received.

There's also a new element of the thermal shipping container that has been introduced with this product. The container allows for the movement and shipment of the vaccine from one site to another and allows it to be managed in the ultra-low temp conditions. There is training required with using this thermal shipping container and staff being able to be trained on the monitoring, the dry ice replenishment requirements, as well as understanding how to manage the product over time, how many times to open the container. And the details have also been part of the training and what we're getting vaccination sites ready for.

There're also complexities with mixing and using the product. It is a little bit different than other vaccines that we've seen as far as the diluent being required, how the product is drawn up, and also how quickly the product needs to be used. Once diluted, we do have a six-hour period in time in which the vaccine needs to be administered, and that has also

been factored in and built into the planning at the administration site level.

Lastly, we do have inventory planning that is underway to ensure that there's sufficient supply available for administration. This includes ensuring that administration sites have actual clinic planning times, that they're able to have enough people to come manage the 975 doses for each of the trays, and the planning for the actual clinics, as well as the planning for the second dose. Since the second doses are required, the timing's 21 days and any cushion that we have beginning or ending from the 19 to 23 days that we saw in the clinical trials.

What exactly that looks like and how that gets operationalized and implemented is also part of the planning factor. Second dose reminders are part of insuring that people come back for that second dose, and additional strategies are also underway. So with that, I'd like to pause and turn it back over to the moderator.

DR. ARNOLD MONTO: Thank you, Dr. Patel. We're going to have time for just a couple of questions at this point. Dr. Levy?

DR. OFER LEVY: Hello. I have a brief question for Dr. Messonnier. First of all, thank you so much for your presentation. It was very helpful. You needed to move very quickly through some very important information about the safety surveillance systems that are in place to monitor the progress of coronavirus vaccine.

I did have a question. You described a number of interlocking national systems that would monitor vaccine safety. I wanted to know if there's any consideration or plans for also integrating these systems with international efforts monitoring coronavirus vaccine safety, for example, World Health Organization, WHO. There's also an international network of special immunization services and others. So that's my first question.

My second question has to do with vaccine

effectiveness. You mentioned some key subgroups that you'll be monitoring vaccine effectiveness in. Those all made good sense. It went by quickly, but I didn't see teens or maybe even eventually younger children listed among those special populations. But I would imagine they would be of interest as well, and I'd value your comments on that. Thank you.

DR. NANCY MESSONNIER: Thank you for easy questions. The answers to both questions is yes. There's actually a WHO coordinated group looking at sharing data for both safety and effectiveness and coordinating across the globe on that. In addition, we are working directly with collaborators in the UK and in Canada to make sure that we're sharing information as quickly as possible, and we're already gearing up to help a number of countries for immunization campaigns.

The answer to the second is definitely yes. I didn't put it on the slide because authorization for those groups was not really up for discussion today, but certainly it will be really important to be able to

monitor both safety and effectiveness in an enhanced way in those groups, period.

DR. ARNOLD MONTO: And the final question from Dr. Kurilla. After that, we'll have to move on.

DR. MICHAEL KURILLA: Thank you. This is for Dr. Messonnier. You described a very comprehensive assessment, aggregation, collation of a lot of safety signals, and I'm wondering the intention for that group -- is that to provide ongoing advice to the people who would be distributing the vaccine, potentially administering it, public health officials, or is that primarily to be focused towards the FDA in terms of refinement of the EUA itself? What's the real focus of all of that safety assessment? Where's it going?

DR. NANCY MESSONNIER: I mean, I think it could be for multiple uses. However, our standing up of an ACIP work group is to be a part of our ACIP recommendations, that is the recommendations for use of the vaccine. CDC and FDA and all the USG partners coordinate, collaborate, work together in the safety

landscape every day on all our routine vaccines. And as you look at our systems, you'll see how intertwined they are. Any information, for example, that we get will be shared quickly with FDA, as well as putting these systems in place so that our Advisory Committee can review it.

I also might say that CDC and FDA are also discussing a contract with NASM -- the National Academy so that we also have them to provide expert independent review of vaccine safety issues that may arise in the COVID-19 vaccination program. So in addition to everything we've set up, we're also setting up that collaboration contract with NASM so that we also have them ready if we need to help adjudicate a safety signal. Thank you.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: Well, thank you to both of our CDC presenters. I'd like now to move on to the presentation from Dr. Steven Goodman, who is Associate Dean of Clinical and Translational Research at Stanford

University School of Medicine. And he is going to be talking about considerations for placebo-controlled trial designs if an unlicensed vaccine becomes available under EUA. Dr. Goodman?

CONSIDERATIONS FOR PLACEBO-CONTROLLED TRIAL DESIGN IF AN UNLICENSED VACCINE BECOMES AVAILABLE

DR. STEVEN GOODMAN: Thank you very much. I want to thank the FDA for inviting me to speak to this Advisory Committee today on one of its most important decisions. And the title on this slide says exactly what I'll be speaking to. Let's see. There we go.

So what are these considerations? Well, there are two, and they're intertwined. First are the ethical considerations, which concern the questions about what is the right thing to do with the placebo group in this case. The second class of considerations are epistemic, concerning what we know or what we believe, which is determined by the strength and

totality of the evidence. That's what's generated by the designs we are already using and the ones we'll use going forward, which might be the most consequential thing that we discuss today. Let's see.

Now, I will be speaking about ethical issues, but I am not a card-carrying or PhD carrying bioethicist. But I've enjoyed working with many, and I want to acknowledge before I talk the contribution several have made to my remarks today, although the views and ethical lapses are my own. They are Professors Nancy Kass and Ruth Faden from Johns Hopkins and David Magnus from Stanford.

Now, there are a lot of questions embedded in what should happen with the designs and particularly the control groups in studies going forward. This slide outlines a lot of sub-questions, but I think the title of the presentation pretty much captures it. If an EUA for this and other vaccines are granted, what do we do with the placebo control groups in this trial and potentially in ongoing and in upcoming trials for the

next vaccine?

Now, I want to start with a set of ethical preliminaries. I'll start with something that seems very basic, but I can't tell you how many committees I've been a part of and that I've watched whose conversations have founded on this simple issue. We're going to be dealing with ethical dilemmas here, but it's worth thinking about what an ethical dilemma is.

So an ethical dilemma is not a choice between right and wrong. That's what we write to advice columnists for. And ethical dilemma is a choice between two actions that are both ethically justifiable under different moral frameworks or principles. In that sense, it's a competition between two rights -- two right actions, which of course is exactly what makes it a dilemma.

We face this is in every clinical trial, but particularly on data monitoring committees there's tension between actions that are good for an individual, which in the current setting might mean

giving them a vaccine immediately, and what's best for society, which might mean holding off on that vaccine so placebo-controlled randomized trials can continue. Resolution of ethical dilemmas always requires compromise to balance the competing dictates and minimizes physical harms or ethical wrongs which are caused by unfairness, violations of autonomy, or actual personal or societal harm.

Now, to continue, our ability to conduct clinical trials, which is to experiment on each other, is something that society gives us permission to do. We don't need that permission to do chemistry or biology experiments. And because the procedures and oversites for RCTs are so structured and standardized, it's easy to forget how fragile that permission to conduct RCTs is. But anybody who's worked as an institution whose research enterprise has been completely shut down because of a single ethical lapse knows that this trust can never be taken for granted, and it's continually earned and re-earned through fair

and transparent processes to determine what's acceptable. And that's what we're doing today and why it's so important that we're doing it in public.

Now, final preliminaries which is ethical acceptability depends often on context or background conditions. Offering a placebo subject the vaccine can be judged quite differently depending on whether the evidence -- depending on the evidence we have about efficacy and safety and whether or not that participant can actually get the vaccine outside of the trial. And both of those are part of the context today.

Now, epistemic preliminaries, I'll start by saying something that shouldn't be too controversial, which is that RCTs, or randomized controlled trials, provide the most reliable knowledge about the relative efficacy and safety of intervention, at least as permitted by the sample size, and follow up time. Obviously, we can't detect safety issues that come up after the RCT closes. A second principle is that reliable knowledge can come from non-randomized

designs.

And Dr. Messonnier just introduced us to some of those. This includes exactly the kinds of things she described: vaccine safety surveillance, all of epidemiology, quasi-randomized design, natural experiment, and understanding of biologic mechanism. These can play a critical role. And finally, there are many things to learn about these vaccines. We've talked about them already. Some of them are best learned through an RCT but not all of them, and there are many things we can learn from these other designs that do not require RCTs.

Now, finally, in the stage setting, there should be no bright line. That is bright lines are almost always unjustified, and they are the enemy of ethical and epistemic compromise. In ethics, this means we can't allow one moral framework or principle to trump another.

We can argue about how one principle takes precedence over another, but it's not helpful to hear

assertions like "It's unethical to deny an effective vaccine to a placebo recipient." Asserting that anything is unethical effectively shuts down the debate and also demonizes people on the other side. And I found it extremely healthy for committees not to use that word at all. There's a corollary epistemology where we can have reasonable discussion about what we can learn and what we can't learn from randomized and non-randomized studies but saying things like "You can't learn anything from a study without randomization," is both obviously not true and inimical to a balanced solution.

Now, what do RCT participants know? Let's get into the issue of ethical obligation. All consent forms and consent processes are required to tell the patient or the participant in the study that the purpose is to produce scientific knowledge that benefits society, not necessarily them directly. They're also told or they trust that they won't be exposed to known serious harm not listed in the consent

and that they can withdraw at any time for any reason and that they'll be given information arising during the trial that's highly relevant to their decision to continue.

This is exactly what is in the Pfizer consent in quite plain language. I've put it up here. I won't take the time to read through it, but it's quite explicit. And we have no reason to believe that the study was misrepresented in any way.

Here in the highlighted area you can see "you're free to stop participating at any time, and the study team will tell you in a timely manner if new information is learned that would change your mind about continuing in this study." And that certainly would be an EUA.

Now, let's talk about -- I'm sorry. I skipped a slide there -- whether there's special obligations to placebo recipients. Obviously, they have exactly the same -- we have the same obligation to them that we have overall to the trial. They're free to withdraw.

And because of that, the trial structure and investigator shouldn't actively deny them vaccine in any way if it became otherwise available to them through a social prioritization and local circumstances. And this is consistent with the FDA position stated earlier. We'll come back to this.

I would also argue that the investigators are not obligated to provide immediate vaccination in the trial before their turn -- of the participant is called out by the trial. First, this is not what they signed up for, and there are many prioritization criteria out there by very, very good groups. And I haven't seen one that includes trial participation as a basis for jumping the queue. It is not considered a reason to get it before somebody else who might deserve it or need to because of higher risk or other consideration.

But it should be reasonable. When a trial participant becomes eligible through societal priority and local ability, that they are then -- can be provided vaccine in the trial context. So in a sense,

they jump to the front of their own line, and that also binds them to the trial. It's a form of reciprocity, and it facilitates further follow up.

Now, what are some issues related to the COVID-19 context that will have relevance to these decisions? The first is the most obvious. We're in a pandemic. It's a public health emergency, which magnifies potential consequences, both positive and negative, and the consequences of knowledge or ignorance and of action or inaction.

I would say that some rules that apply in peace time might have to be modified in war, and we're in a bit of a war right now. But I want to focus specifically on the health risks to an individual. Given the recent numbers -- not yesterday's, which are particularly terrible with over 3,000 reported dying -- but those in the last few weeks, a randomly chosen U.S. citizen has an average risk of dying from COVID in the next six months -- that is by the end of May -- of roughly one in 1,000 and the risk of hospitalization of

roughly about one in 200. These numbers obviously vary widely by individual, and they don't include the harms from non-fatal COVID. But they're highly ethically relevant, and let's start to talk about that.

So if the risk of death in the U.S. in the next six months is around one in 1,000, that means the maximum benefit of the vaccine for an individual, at least with respect to mortality, is also one in 1,000 or 0.1 percent. So imagine if we had a drug that purportedly raised cancer survival from 40 percent to 40.1 percent. If there was more to learn -- and we do have that here -- that's a setting where we would typically allow many placebo-controlled trials. We see this in meta analyses all the time with multiple trials -- placebo-controlled trials of agents with therapeutic benefit orders of magnitude larger than this.

So while this risk obviously has huge population impact, in terms of trial ethics, it's not the kind of risk that incurs a great ethical debt to the placebo group or a prohibition on further placebo-

controlled trial. Also, unlike a therapeutic drug for patients with a disease who can't change their own prognosis, many but not all individuals can take actions that reduce their own risk of death from COVID, like masks and social distancing. So as long as there's still important things to learn about the vaccine, placebo-controlled trials should not be regarded as unethical. However -- a big however -- they might be infeasible, and that is a big issue because people may not be willing to either remain in the study or to enroll. But it's very important to not conflate the feasibility with the ethics.

Now, in terms of the vaccine context on what we know, I'm actually not going to spend my time on this. You're going to hear -- you've already heard a lot about the Pfizer vaccine. The only one I want to highlight is that if a participant wants to unblind themselves in a trial they can. If they have the resources and knowledge about which antibody -- commercial antibody test would unblind them, some of

them are to the spiked protein which would unblind them. Others it's a nucleic acid, which might not.

Now, in terms of the vaccine context or background position, what we don't know -- well, this has actually already been covered. There's a whole raft of things that we don't know yet and that we want to learn, both from continued RCTs and also from observational studies. Now, I want to outline a possible adverse scenario. If placebo participants who want vaccine when otherwise available and eligible are not given access within the trial in the name of scientific rigor, there may be many who respond to appeals by investigators not to seek vaccine even if available to them.

And to them, this argument doesn't apply. And we've seen that willingness to hang in in studies with placebo controls in many other trials of even greater personal consequence. So it's not at all unlikely that there would be a sizeable number of people who wouldn't do that on appeal. But some participants at higher

risk will want the vaccine as soon as it becomes available to them.

And if they can't get it through trial mechanisms, many will lose trust in the investigator and the trial itself and may leave the trial without further follow up. They may seek vaccine outside the trial, and as more vaccines come on the market, perhaps they'll get another one that's available recently with very uncertain effect. This will get a lot of publicity, meaning that recruitment to future vaccine trials will be that much more difficult because of a collective loss of trust.

So some might appeal to the experimental status of the vaccine under the EUA as justification -- as ethical justification for maintaining a placebo control. I understand why this has salience within the FDA, but I suspect that this distinction will not get much traction among future or current -- current or future trial participants when literally millions of people are being urged to get vaccinated as quickly as

possible. The point is that once the vaccine's widely available or any vaccine is widely available and encouraged, the ability to maintain double blinded placebo control groups voluntarily for more than a nominal period, by which I might mean perhaps a few months, will likely not be under the control of the sponsor or the FDA. And some efforts to do so could undermine future trials as people don't trust that their interests will be watched out for.

Now, I want to mention an important countervailing view, which is that many people out there, as we well know, are very wary about an expedited approval process and will refuse a vaccine that they believe to be under-tested. They want to see those trials going through their planned end, but unless these people can be found and are willing to enroll in placebo-controlled trial, the argument about the feasibility of the trial still hold.

Now, what's the Pfizer proposal for continuation? Now, it implicitly recognizes this

reality, and it's consistent with everything I've discussed so far, except in one important regard. First, they propose urging as many people in the trial to stay as long as possible, which I think is the right thing to do. But for placebo participants who become eligible according to local or national recommendations -- that's an important condition -- and who ask for the vaccine, they propose unblinding them and vaccinating.

For those who stay in the trial blinded, it's proposed that everyone be vaccinated after six months and followed for an additional 18 months to the trial's planned end. This is coupled with a robust observational pharmacovigilance plan for long-term safety monitoring that augments what the FDA and CDC are doing. While not unreasonable, I think that we have to remember that this design will not only unblind placebo recipients. It will also unblind vaccinated participants who make the same request because, of course, they won't know. And once unblinded, risk behavior can change. Many of the benefits of

randomization within the trial are lost.

So is there an alternative? And I would say there is and should be considered. There are two alternative designs that achieve the same ethical goals without compromising far less -- without compromising on the epistemic ones. That is we can give people vaccine who are eligible and who want it but maintain the blinding, thereby preserving trust that the investigators and regulators care both about the science and the participants.

And let's talk about those designs. One is called deferred immunization. It's been presented in a variety of settings and gotten coverage, also a blinded crossover design. And the second are active control designs, which are really not the issue for today, but I'll discuss them briefly.

The first of these was developed by a biostatistician at the NIAIB, the NIH, named Dean Follmann. It involved blinded crossover designs, and the idea here is that the placebo -- when either a

placebo or vaccine recipient becomes eligible for a vaccine or requests it -- exactly the situation that the Pfizer proposal describes -- that the placebo recipient gets a vaccine, and the vaccine recipient gets a placebo without being told what they were originally. So the blind is maintained. And then they are followed forward. So they stay within the trial confines and to some extent also protected by the randomization.

As I mentioned, the second design is active control. At some point in the evolution of vaccine testing, we may no longer be able to conduct placebo-controlled trials of any type in settings where vaccines were available. Although it's not a question for today, at that time, when there are a lot out there, a comparison vaccine with reasonably well-established properties may have to be used in one arm in those areas where they're a variable. But we're not at that stage yet, but we may be within the next year in some countries.

Now, in countries or regions where vaccine has seen poor distribution it may still be possible to conduct placebo randomized trials, but that has ethical complications of its own. And I'm not going to get into that here. I want to talk just a little bit more about the deferred randomization scheme, and you see that in this picture. The idea is that we'd start with a vaccine and placebo arm, as we already have. And then at the point when people are eligible and ask for the vaccine -- you have to have both conditions -- that's the point where a blinded crossover occurs.

Because every participant is ultimately assigned to the vaccine arm at some point, this design actually in some situations -- in very plausible situations -- can have greater or equal power to detect the duration -- the sustenance of immunity more than a standard 50/50 RCT. And you can sort of see that in the figure where you see the contrast between the vaccine efficacy in the width of the bar -- in the delayed vaccine arm compared to the waning efficacy in

the original arm. And this increases over time, and these can be compared statistically. So you can see how this can work for vaccine efficacy.

But, of course, it decreases power to detect some other things like long-term safety issues and some other important parameters, but it doesn't lose them as completely as designs where subjects are unblinded and effective randomization is lost. So if the standard 50/50 RCT is not reasonable or feasible, which I believe it very quickly won't be, this design is far better than any that would break the blind and break the randomization. We can, of course, also reduce some of the ethical tension in any placebo-controlled trial by increasing the allocation ratio to the vaccine arm, but that may not be enough to solve the enrollment problem.

The next slide shows another picture of this deferred vaccination schema, and it shows that it's possible -- you see the crossover on the right. On the left-hand side, we have the trials as they've been

designed so far. On the righthand side you see what they look like after the crossover, which is that everybody's been immunized. But it's possible statistically to impute an unvaccinated control group to help estimate secular trend.

So to finish up, I want to summarize that these alternative designs require compromises, the kind of compromises I talked about before on both the ethical side and the epistemic side -- that is the evidence. Ethically, placebo recipients don't get a vaccine as quickly as some might want, and this will become more of an issue going forward as new vaccines need to be tested with multiple ones already available through EUAs. But of course, those subjects are not being forced to enroll, but the ones who do enroll can expect to get immunized at a certain number of months going forward. As noted, placebo-controlled trials may continue to be possible in areas or populations for whom vaccines are not available, but that is complicated for other reasons.

Finally, on the epistemic side with this crossover designs we don't learn as reliably or as quickly about long-term safety and infectiousness and other factors. Although, we still might learn as much or more about durability when compared with a trial that continues with the placebo arm. But as I said, that trial may not be doable. We might not have the perfect design going forward and continued blinded observation of the deferred vaccination group can still be tremendously informative and potentially more informative than one with broken randomization, particularly in combination with observational studies of the population that we've heard about today.

By reducing the ethical tension within the trial and by retaining the trust in trial testing system, it provides a way further for future studies of other vaccines. So none of these are the last words on this very difficult and complicated subject, but for today, these will be my last words. So I hope this will be helpful to you, and I welcome your questions

and comments. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Goodman. You've given us a lot to think about and to discuss. I just wanted to start by raising one question. With the blinded crossover design, when would that take place? When an individual becomes -- reaches the priority listing for their group, or would that be at the time of issuance of the EUA?

DR. STEVEN GOODMAN: So this is a subject of tremendous controversy and discussion. For the reasons I've already outlined, I don't think it should be -- and this is my opinion -- at the moment of the EUA because otherwise they are jumping the queue, and I discussed that earlier. I believe it should be when the -- for those subjects, they come up on the social -- you know, they come up as they would come up in terms of priorities for the vaccine and it's available to them in their area -- that is they can get it outside the trial.

As soon as they can get it outside the trial,

then this would kick in because we want to keep them in the trial. If it's given at another time, we're basically giving them priority over other populations that have been deemed to be at greater risk or greater need. And the price I think we have to pay by compromising the trial I believe would be too high, and we don't have -- again, I made this argument earlier. I don't think we have that special obligation to give them the vaccine immediately. Those are my views.

DR. ARNOLD MONTO: Okay. Thank you. I think we'll defer questions about how feasible this is to the sponsor after the sponsor's presentation. Next is Dr. Levy. And please unmute and show yourself if you'd like.

DR. OFER LEVY: Sorry. That was an error. I don't have a question.

DR. ARNOLD MONTO: Okay. Dr. Meissner?

MR. MICHAEL KAWCZYNSKI: Go ahead, Dr. Meissner.

DR. STEVEN GOODMAN: I guess I answered all

questions.

MR. MICHAEL KAWCZYNSKI: Should we go to the next one?

DR. ARNOLD MONTO: Yeah. Dr. Chatterjee?

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Goodman, for your presentation. It was certainly thought-provoking. I have a question with regard to the current study participants. By reviewing the briefing documents, it appears that there's a difference between participants who received the active vaccine versus placebo recipients in terms of adverse events that they experienced. And so there's a potential that people who are participating in the trial can actually guess which arm they were surmised to.

DR. STEVEN GOODMAN: Yes, absolutely. Yes.

DR. ARCHANA CHATTERJEE: Yeah. So is there then a possibility that those who believe that they were placebo recipients might wish to withdraw in greater numbers and that that would then compromise the

study as well?

DR. STEVEN GOODMAN: Again, if they are -- it absolutely could, so even going forward it could. And that would be an issue for the statisticians and for the FDA. The point of this particular proposal is this would give them an avenue not to withdraw, that is stay within the trial under these conditions. Now, if they didn't want to wait for their allocation to become available or eligibility locally, withdrawing wouldn't do them anything. It wouldn't get them the vaccine any earlier, so there would be no motivation to withdraw.

And also, I do think that the majority of people who signed up for these trials did so in good faith and with altruistic motive. I do believe the vast majority want their contribution to produce a valid scientific result. So I don't think self-interest completely in any way dominates. And again, yes, I do believe that there's a fair amount of unblinding just due to reactogenicity of the vaccine and obviously non-reactogenicity of the placebo. But

this -- again, at the time when they might be able to get the vaccine outside the trial, this would give them a way to still contribute to the science of the trial without leaving. I don't know if that answers your question.

DR. ARCHANA CHATTERJEE: No, that did, and I was thinking about the people who would meet the priority criteria obviously. They would be the ones who would want to withdraw if they thought they were in the placebo arm.

DR. STEVEN GOODMAN: Correct. And I do believe -- that's what I said. I do believe that could happen.

DR. ARNOLD MONTO: We've got a lot of questions. I think we -- and what we're going to do is I'm going to ask all the speakers to please be available during our discussion because we may have additional questions that come up at that point. I'd like to move on to Dr. Kurilla, please. We've got a lot of hands raised and no time.

DR. MICHAEL KURILLA: Thank you, Arnold. Great presentation. So the blinded crossover design looks quite feasible. However, the caveat is that it will take -- it does take longer to get to the answer. Did I hear that correctly? That's number one. But would we also be facing a first mover effect where this would basically dictate future trial designs short of any vaccine having the full BLA going forward? So everyone else would have considered this option as the de facto approach.

DR. STEVEN GOODMAN: Yeah. That's a really good question. That's why I emphasized that -- I'm sorry. I see you talking, but I don't hear you. I'll just answer what I heard.

I can't judge exactly what will happen in the future because fact patterns are going to change, so I hesitate to predict too much. It is possible that this might represent, as we go forward, a default design that reduces the ethical tension of these trials as vaccines, as I mentioned, become available in the area

of potential enrollees in the trial. And what we'd then be asking them to do is not completely deny themselves a vaccine which they could just go out and get if they themselves are eligible but just defer it for a few months. It might be two months, three months, four months. And that might be less of an ask. I can't say whether it will become the default.

Again, it's going to be a while before enough vaccines of any type, no less just this one, are rolled out even in the U.S. Remember also that these trials are going on all over the world, so the U.S. places where -- they will not always be occurring in places where vaccines are otherwise available for quite a while. So it is possible we might evolve.

I do see that there's going to be a staging where there's going to be a point or places where we cannot any longer do the placebo-controlled randomized trial. We might move to this. And then ultimately, as I said -- and it might be a year or two from now -- have to move to active control. That's the evolution I

see.

Whether you're committing to this design going forward harder to say. That's very complicated, and, again, it's going to depend a lot on vaccine distribution and what we learn about these vaccines. If we learn -- if there start to be safety signals that we're not seeing right now, that could change the dynamic dramatically.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: I'm just going to allow one more question because we have to start at noon Eastern for the public comment, which is difficult to control otherwise. So Mr. Toubman, you'll be the last question, and we're going to come back to this discussion as part of the afternoon. And I think we will really want to pick up where we've left off on some of these issues at that point. So Mr. Toubman?

MR. SHELDON TOUBMAN: Thank you. I really appreciate the presentation. On the blinded crossover design, if I understand this, basically you solve the

problem of maintaining blindness. You don't have to unblind, but you do lose the placebo. That group that's been put into that blinded crossover system, they won't have a placebo group (audio skip) for purposes of (audio skip).

DR. STEVEN GOODMAN: That's right. You lose the contemporaneous placebo. That's right. You retain the value of having had a placebo at the beginning, though, because of deferral. And if there's a waning -- particularly on the issue of waning immunity, obviously that difference might continue over time. So you retain some of the value of having a placebo at the beginning but not all of the value because things like, particularly, safety and other issues which might not be contingent just on the specific timing of when you got the vaccine. You will probably lose that or diminish that.

You don't completely lose it. It depends on the characteristics of what it is you're measuring. There are many things we can look at still with this

design, but that's why it has to be these designs coupled with the observational designs outside, which is obviously both what Pfizer's proposed but also what the CDC and the FDA are also doing.

So there's many things that can be learned outside the trial that we might have been looking to the trial to provide. Now, we'll be depending more on observational designs if we move more to these trials. So we don't lose all the benefits of placebo group, but we do lose some of them. But that may not be a practical option, which was my point.

MR. SHELDON TOUBMAN: All right. Your position's that we should not move people into the blinded crossover design until they're eligible in their particular societal group for getting it anyway. I will say that we have gotten a lot of comments from folks who are in trials -- like, dozens of them -- and their line seems to be "Well, if EUA is granted, I should be (audio distortion)." I'm not asking you to opine on that. But my question is your view is you

should wait until it's readily -- their group comes up. But if EUA didn't cover them at all -- that's one of the possibilities we'll talk about later -- would that help in the ethical determination that, yes, they should definitely wait because, after all, EUA has not been granted for their group yet anyway?

DR. STEVEN GOODMAN: I haven't thought through that whole chain. All I will say is that they don't -- again, I mentioned this previously. I don't think that they're -- it wasn't part of the initial contract. They understood that they could do without the vaccine for much longer, in fact, then they probably will have under a deferred policy. And they still get priority under this plan. It's just they get it first within their own priority group, so it's not that they are not owed anything.

There is a reciprocity here in that when their, in a sense, turn comes up they get it first through the trial mechanism. And so they're not completely -- they're not disadvantaged by being in the

trial. In fact, they're advantaged, just maybe not as much as they might want by demanding it today. But as I said, I don't think the ethical calculus is such, and other groups have not thought it such, that they are necessarily owed that just by virtue of being in the trial. But they do get a benefit.

DR. ARNOLD MONTO: Okay. Thank you very much. I know these are very difficult situations and scenarios that we will need to be talking about again during the first part of our discussion. I apologize also to those people who I haven't been able to call on. You'll have your chance during the discussion because there's going to be a lot that we're going to have to talk about in the first part of our two-hour period that we have assigned this afternoon. I am not sure -- Prabha, when should be come back because I know some of the public presenters are ready to go at noon Eastern? Prabha or Kathleen?

MR. MICHAEL KAWCZYNSKI: So we're scheduled to come back at -- we're originally scheduled to come back

around 12:00, but we still have to call in all the public speakers. So let's just schedule it for right now, as long as -- Prabha, are you there?

DR. PRABHAKARA ATREYA: Yes, I am here.

MR. MICHAEL KAWCZYNSKI: Okay. Go ahead.

DR. PRABHAKARA ATREYA: So we are scheduled to start at noon time, so are they all lined up now to go at noon or do we have five minutes extra to give them?

MR. MICHAEL KAWCZYNSKI: No, I need to call them in all now. So we will project to be scheduled for a 25-to 30-minute break, but we have to confirm all the OP speakers come in. So let's at this time -- Prabha, if you agree, we'll do a 25-minute break, but we may have to extend it a little to make sure we have time to get everybody in. Okay?

DR. PRABHAKARA ATREYA: Yes, okay.

DR. ARNOLD MONTO: Okay. That's the guidance I needed. Thank you. So we're going to try to resume around noon Eastern.

DR. PRABHAKARA ATREYA: Thank you.

MR. MICHAEL KAWCZYNSKI: Thank you. So with that, we are going to take a break.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Hold on, Arnold. Alright. And welcome back to the 162nd meeting of the Vaccines and Related Biological Products Advisory Committee break. I'd like to now hand it back over to Arnold. Arnold, are you ready?

DR. ARNOLD MONTO: I am. I'd like to welcome everybody to the open public 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, 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 a sponsor, it's products, and if known, it's direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodgings, or 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. Prabha.

DR. PRABHAKARA ATREYA: Good afternoon everyone. This is Dr. Prabhakara Atreya. I am going to conduct the open public hearing session and I will read your names in order. And then, when I call your

name please unmute your phone and then start speaking. And you have three minutes to complete your remarks. Thank you. The first name is Dr. Kermit Kubitz.

DR. KERMIT KUBITZ: Hello. These are my comments to the Vaccine Advisory Committee on the BNT162b2 Coronavirus vaccine. Cover efficacy, structured benefit-risk and follow up. I have no conflicts except for a lot of elderly relatives. Next slide.

The Pfizer vaccine appears efficacious based on 95 percent relative reduction in infections and T Cell responses comparable to human convalescent sera, see Figure 2 page 22 and Figure 4 page 24. Some uncertainty is introduced by the possibility of mild asymptomatic infections, including among placebo patients, feelings of pain or injection site effects that may have caused more vaccinated participants to be tested than placebo recipients. Next slide.

Benefit-risk. I have reviewed the available evidence. And as a Caltech graduate, despite the

uncertainties, the structured benefit-risk of Pfizer BNT162b2 is very positive. The Coronavirus, as we have heard, is a serious medical condition with 3,000 daily deaths. While there are therapeutics, there are no prophylactics against COVID-19.

Even in the event of approval of the Pfizer vaccine, limited supplies will require EUA of other efficacious vaccines when available, such as Moderna or others. Benefits of the vaccine include prevention of COVID-19 after the second dose, prevention of severe COVID-19, and preventing COVID-19 after the first dose. Risks appear to be mild injection site pain, fever, or fatigue.

Increased reactogenicity for recipients over 55 is more than offset by the benefits of preventing COVID-19 cases in older adults with weaker immune systems. I note that allergy-susceptible persons should be informed of any issues in the EUA vaccine following approval. The net benefit is highly positive. I would recommend the vaccine to my siblings

over 80 and my relative in an assisted living facility where there are have been three cases for staff and three cases among residents.

There is a need for follow up of vaccination effect including how long after immunization patients are protected, whether the vaccine prevents infections which cause further transmission, and how any violations of cold-chain supply, dilutions, shaking, or administration affect efficacy. Thank you, Dr. Fink, Dr. Gruber, Secretary Azar, Dr. Gans, and Dr. Messonnier. They need this vaccine yesterday.

DR. PRABHAKARA ATREYA: Okay. Great. Thank you. The next speaker is Diana Zuckerman.

DR. DIANA ZUCKERMAN: Yes. Hi. Can you hear me?

DR. PRABHAKARA ATREYA: Yes.

DR. DIANA ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Next slide. Our center scrutinizes the safety and effectiveness of medical products and we

don't accept funding from companies that make those products. My expertise is based on my post-doctoral training in epidemiology, and as a faculty member and researcher at Vassar, Yale, and Harvard, and also previously a Fellow in Bioethics at Penn. I've also previously worked at HHS and the U.S. Congress. Next slide.

Today I'm going to focus on two major concerns on how we can improve the data that are already available. Number one, the two-month median follow up is just too short to have long term safety information and long-term efficacy information. So it's essential that the randomized control trial be continued.

Number two, there's a lack of diversity in COVID cases. There were zero black cases in the vaccine group and only seven black cases in the placebo group. And there were zero cases that were ages 75 and up in the vaccine group and five in the placebo group.

And it was very disturbing, Wall Street Journal did a chart saying it was 100 percent effective

for Black patients, for example. So that's one of the reasons why we need more people, so we have reasonable data. Next slide.

There are also too few severe cases to draw any conclusions. There were only four severe cases after the second dose. That's just too few to conclude anything. Next slide. Long term care patients were not in the study. There were about 800 people, ages 75 and over in the study, but only five were cases.

So we want to save their lives but how can we ensure informed consent to nursing home patients when we have no data to provide? And how many frail, elderly or their family members can make an informed decision based on so little information? Next slide.

We need long term data to fully understand if the benefits outweigh the risks for frail patients, and for all races and ethnicities, and for all patients. And that's why continuing the randomized control trial is so important. Next slide.

In conclusion, the EUA is not approval and it

should have more restrictions than you'd have for approval. So FDA should require continuation of the RCT while targeting EUA to priority populations, especially healthcare workers. I agree, don't let anyone in the placebo group jump the queue.

Second, EUA should not allow off-label use for non-priority groups whether they're celebrities or anybody else. Off-label use could potentially occur under FDA's expanded access program. And last, FDA should delay access to vaccines by the placebo group unless they are in the priority populations.

And I am concerned that the blinded crossover would be informative if the vaccine is not long term efficacious. But if it was efficacious long term, we would lose that information in a blinded crossover. Thank you very much for the opportunity to speak today.

DR. PRABHAKARA ATREYA: Great. Next speaker is Peter Doshi.

DR. PETER DOSHI: Hi. This is Peter Doshi. Hopefully, you can hear me. Thanks for the chance to

speak. For identification purposes, I'm on the faculty of University of Maryland and a medical journal editor with the BMJ. I have no relevant conflicts of interest and no one has paid for my attendance. Slide two, please.

My experience has been that careful review of a large trial takes considerable time and effort. As FDA has already reviewed the data, I'd like to know whether FDA's confident in the data collection for the primary endpoint. Specifically, that any unofficial unblinding did not affect the result. And that fever and pain medications did not mask symptoms, thus preventing case detection. I didn't find answers to these questions in the FDA's briefing documents. Slide three.

A dramatic difference in rate of side effects between vaccine and placebo raises questions about how well these trials could be observer-blinded. With a subjective endpoint like symptomatic COVID, blinding is important. But it seems fair to think that people

could make reasonable guesses as to which group they were in. Slide four, please.

In the real world, the mantra has been to test, test, test but this wasn't the case in the trial. The study protocol says, in the seven days after vaccination do not test unless, in the investigator's opinion, the clinical picture suggests COVID rather than vaccine side effects. This basically amounts to asking investigators to make guesses as to which intervention group patients were in. My question is, was this kind of judgement ever applied in the days it could affect the primary endpoint? And now I'd like to skip to slide six in the interest of time.

Possible unblinding would matter less if the trials had been designed to directly test the vaccine's ability to reduce deaths, ICU use and hospitalizations as most people assumed the trials were set up to do. It's great when the data look encouraging, but trials should be directly testing the endpoints that matter.

Then there's the duration of protection issue.

A vaccine that delivers a 95 percent relative risk-reduction of COVID two to three months after vaccination is one thing. But for the many people who lack natural immunity, and don't get exposed to the virus soon after vaccination, protection needs to last much longer. After six months or a year, will the vaccine still meet the FDA's 50 percent effective requirement? The trials just don't have sufficient data to say.

Keeping the trials going with placebo-controlled follow up will help answer the many crucial questions that remain. For those that do not wish to wait for clear evidence that benefits outweigh risk, an expanded access program can be set up. Access doesn't require authorization. And I just want to end by saying that whatever FDA ultimately does, the full trial data must be made publicly available. Thanks for offering me the time to speak.

DR. PRABHAKARA ATREYA: Okay. The next speaker is Rossi Hassad.

DR. ROSSI A. HASSAD: Thanks. Thank you. I am Rossi Hassad a professor at Mercy College with expertise in epidemiology, statistics, and mental health. I hereby declare no known potential conflict of interest. Next slide.

This vaccine is reported to have an impressive overall efficacy rate of 95 percent consistent across key demographics. However, the primary efficacy endpoint of the trial was symptomatic COVID-19 infection. Participants who may have developed asymptomatic infection were not identified in this trial. Therefore, if as expected an Emergency Use Authorization is issued, the spectrum of COVID-19 infection that this vaccine is efficacious against must be emphasized. Next slide.

Adequate statistical power is necessary for differentiating between an actual vaccine effect and one that occurred by chance. The power of this trial was calculated as 90 percent to detect an overall effect for vaccine efficacy and may not allow for

formed conclusions regarding subgroup differences. Next slide. As reported, there were no serious safety concerns, which is quite reassuring. However, there were frequent mild and moderate adverse effects which are recognized as common side effects of vaccines. Next slide.

Additionally, participants were blind as to whether they received the vaccine or placebo. But given the common awareness of vaccine side effects, unintentional unblinding may have occurred and this can potentially inflate estimates of vaccine efficacy. Next slide.

In conclusion, the potential benefits of this vaccine outweigh the identified risks. Therefore, I support the issuance of an EUA with the stipulation that the vaccine can protect against symptomatic disease. But at this time it is not known if it prevents infection and transmission.

Contraindication for those with a history of severe allergic reactions is plausible and should be

included in the EUA as well. The continuing need for non-pharmaceutical interventions, particularly mask wearing, should also be noted. Finally, ongoing monitoring of this vaccine is imperative. Thank you.

DR. PRABHAKARA ATREYA: Okay. The next speaker is Evan Fein.

MR. EVAN FEIN: Hi. My name's Evan Fein and I'm a Phase 1 participant in the Pfizer-BioNTech trials that was conducted by researchers at NYU. I have no financial or other conflicts of interest to disclose.

I'm speaking today because after conversations with friends, family, and coworkers I thought it was important to share my experience in this trial and to do my part to help ease people's fears about the vaccine. I think I got a real vaccine and not a placebo because of mild adverse effects such as fever, chills, and pain in the injection site after the second injection. After reporting the side effects, I was called repeatedly by the doctors and researchers at NYU to see if I was okay, and I was.

Nothing felt rushed and I never felt like a guinea pig. The question that everyone asked me is, well what happened in the long term? Are there any long-term side effects? And it's been more than five months now since my first shot and I can happily report that there are none.

Since I participated in the trial, I've helped out my older parents, I've gone to work in person, and I've exercised in small groups, and I haven't gotten COVID-19. I also want to emphasize that these activities do not represent changes of behavior that would alter the integrity of the clinical data. These are life activities that I have to do anyway. Not all of us are able to lock down and stay at home indefinitely.

I'd still do my best to follow health rules and safety precautions. I understand the concern about whether or not people will trust the vaccine, but there will always be some hold outs. Most Americans will take the vaccine voluntarily as long as we're honest,

don't talk down to them and treat them like autonomous adults. But right now, demand for the vaccine exceeds the supply. The skepticism of some does not justify delays for others who desperately want to take it.

The best way to get people to take the vaccine is to lead by example. I don't think that the problem was that this vaccine was rushed, the issue is that other important innovations are slowed down too much by delays in scheduling, lack of funding, and other bureaucratic rules that do little to enhance safety protocols.

If Pfizer, BioNTech, Moderna or anyone else has an RNA product that can immediately help people with cancer, dementia or AIDS, the FDA should accept the data on a rolling basis and work with these companies to get to and complete Phase 3 clinical trials within a year or two. Five to ten years for these trials is simply not good enough. Pfizer has just set the gold standard for future clinical trials. Let's live up to this.

Now, this is an emergency, and the burden of proof is on those who don't want to authorize the vaccine. Absent compelling reason not to authorize it, it is simply immoral and unethical to deny the vaccine to healthcare workers or first responders who want it. An EUA must be granted and it must be granted tonight. As of yesterday, the daily death toll for COVID-19 exceeds the death toll on September 11, 2001. Delays on December 10th will be more deaths on January 10th. In the words of Todd Beamer, let's roll. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Angela Rasmussen.

DR. ANGELA RASMUSSEN: Thank you for allowing me a few moments to speak. I'm a virologist and affiliate of the Georgetown Center for Global Health Science and Security. I have an advisory relationship with Seamans but I have not been compensated to appear today. I'd like to offer some comments on how serology testing might better inform our knowledge of how these vaccines are working after they are rolled out to the

public.

So this expedited process has moved considerably faster than the typical vaccine development timeline. And as such, we are inherently limited on the breadth and scope of data that's available on duration, durability, and effectiveness of the immunity as well as the variability of different vaccinee's respective immune responses.

Due to exclusion criteria in the clinical trial itself, there's also limited data available on minority and underserved populations as well as pediatric populations, pregnant women, and the elderly. And we don't really know a lot about how these broader populations will develop antibodies to the vaccines.

Also with the limited supply of vaccines, at least initially, it's going to be really critical to determine who has already been infected with SARS-CoV-2 in order to conserve the vaccine for equitable access for others in the same priority category.

Because this rollout will be so highly visible

and pivotal, we really need to address potential problems such as outbreaks in nursing homes, hospitals, schools or at other at-risk populations due to a failure to seroconvert. And serology testing could really help limit all of these issues. Next slide, please.

Serology testing could help at different phases also, before and after vaccination. But prior to vaccination, serology testing could assist in prioritizing individuals for vaccination as I just mentioned. Also, establishing a serological baseline in the population and help ensure that a scarce supply of vaccines initially reaches the most vulnerable people. Shortly after vaccination, it can confirm initial neutralizing antibody responses to the vaccine.

It can also help ensure that antibody response clears the threshold for protective immunity. And over the longer term, three, six and nine months after vaccination, it can confirm the persistence and duration of immunity. It can also provide the means of

a bridge trial to additional populations and subgroups.

Finally, it can assess the protective efficacy of vaccinations by distinguishing antibodies from vaccinations versus antibodies from natural infection. So by looking for anti-nucleocapsid antibodies, you could actually determine if people who have been vaccinated have been infected after being vaccinated.

And finally, annually after vaccination, we can assess better the persistence and duration of immunity. It can also inform the requirements for future vaccinations that are developed on an accelerated timeline such as this one. Thank you so much for allowing time to speak.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Jared Krupnick.

MR. JARED KRUPNICK: Thank you. Before I begin, your next presenter, Dr. David Berger alerted me that he can't get back into the conference. If you could resolve that for him, so thank you. So slide number one, please. My name is Jared Krupnick. I'm

the President of Uniting for Action and the founder of the Vaccine Considerations Project. I don't have any conflicts of interest to share. Slide number two, please.

As you can see, the Vaccine Considerations Project has been created to highlight health and safety throughout the COVID-19 vaccine evaluation process. I want to acknowledge and thank the incredible team behind all this work. Thank you, Dr. Eric Brown, Dr. David Berger and our incredibly talented, committed, and rapidly growing team of graduate students. Slide number three, please.

I don't have to tell you about the challenges this committee and this Agency have been facing, you're living those challenges. I'm bringing up the challenges to highlight that amid all the different reasons for vaccine hesitancy, what remains universal is that widespread concerns must be adequately addressed in order to ensure sufficient buy-in by public health experts, medical professionals, and the

public. Slide number four, please.

You're seeking to establish trust and confidence in any vaccine you authorize and in the evaluation process by being rigorous, comprehensive, and transparent. There are limits to what can be addressed in a meeting. We're working hard to help you expand those limits. We're creating new ways to organize and share information.

Here you can see how we've thoroughly analyzed the transcript of your previous meeting to extract specific concerns expressed by each individual committee member. We're providing the links to our website, vaccineconsiderations.com, where the full process transcript is available for anyone to see. Slide number five, please.

As you can see on this slide, our team has plotted specific concerns from specific individuals to develop a matrix of concerns. By plotting each concern as a row and placing each of the committee members in separate columns, you can use this matrix to quickly

and easily see which members share concerns, and which concerns have yet to addressed or fully resolved.

You can use this document as a living document where each member can continue to add and update their concerns offline, and the FDA staff and other committee members can address those concerns. By making this public, things won't fall through the cracks. This reassures the public and the professionals that are relying on you. The matrix of concerns is available to all at vaccineconsiderations.com. Slide number six, please.

We're using this spreadsheet as the model to demonstrate the concepts, but a spreadsheet is limited. That's why we spent over a year programming a custom platform called "Information for Action" that provides this type of functionality at scale. Our team is reaching out to stakeholders all around the country, experts, organizations, and associations, to build and organize a central repository of concerns.

We want to invite and encourage this

committee, and the FDA staff, to utilize these technological tools to effectively address concerns, build trust and reduce hesitancies. If you appreciate what we've shared we'd like to connect with you. Please reach out to us at team@vaccineconsiderations.com. Thank you. My team and I look forward to working with you.

DR. PRABHAKARA ATREYA: Great. The next speaker is Mr. David Berger, Dr. Dave Berger.

DR. DAVID BERGER: Hello. Thank you for allowing me to speak today. My name is David Berger. I am a board-certified pediatrician. I have no conflicts of interest.

I am one of the few pediatricians in Florida who does not discharge families from my practice if they have vaccine hesitancy or do not wish to follow the recommended CDC schedule. My comments today are very mindful of the strong, overall benefit our nation will get when most of us have immunity to SARS-CoV-2. Next slide, please.

My presentation today is about vaccine hesitancy and steps that can be taken to increase confidence in the COVID vaccine program. And this should be slide three by the way. It is very important that we see ongoing complete transparency about the vaccine in terms of both safety and efficacy. We have seen reports that up to 50 percent of Americans, and 30 percent of physicians, have some level of hesitancy about COVID vaccines. We must allow for meaningful public scrutiny to build public confidence in the vaccine program. Next slide, slide four.

True informed consent has always been at the core of how I practice medicine. As doctors, we have a duty to inform our patients about the benefits and risks of any medical procedure. If a person feels she is not given sufficient information about a treatment, how can she provide informed consent? I also think it's important to respect people who have concerns about hesitancy about vaccines. I often find that hesitant families will proceed with vaccines if they

don't feel like their concerns were blown off or minimized, but instead were respected and tended to. Slide five.

While there are many subpopulations that should be studied for increased chances of vaccine side effects, there is particular concern about those with preexisting, allergic, hyper-inflammatory and autoimmune conditions. The Pfizer data shows that four individuals who received the vaccine developed Bell's Palsy whereas there were no incidents in the placebo group. On the first day of England's vaccine program, their government had to tell people not to take the vaccine, the Pfizer vaccine, if they have a history of significant allergic reactions after two significant anaphylactic reactions were seen in recipients. Slide six.

It will be difficult to quickly and fully track all 50 states to find the real frequency of adverse reactions. It is important that we have a strong federal program to coordinate this. Please

ensure a plan for this. Please provide data for us to know if people who have had COVID infection already have an increased or decreased risk of a vaccine reaction. Please provide comparative data between the different vaccine products to determine if any brand may have more or different reactions than other brands. Slide seven.

I implore you to put in place a very long-term post-vaccine surveillance program. Many autoimmune or hyper-inflammatory conditions often take a while to develop significant enough symptoms for a patient to seek medical help. Slide eight. It is also important to have a robust surveillance of COVID IgG antibodies so we will have a way of knowing if immunity is waning. We need to know what is considered a protective antibody level for COVID-19 just like we have for other vaccine titers that can be commercially tested. Slide nine.

If the FDA can increase our level of confidence, hesitancy will likely decline and the COVID

vaccine program will have a better chance of success. It will take many good people to defeat COVID-19 and I hope I can help you make a difference. Next slide. Thank you very much. I appreciate the time.

DR. PRABHAKARA ATREYA: Okay. Thank you, Dr. Berger. The next speaker is Sidney Wolfe, Dr. Sidney Wolfe. And he does not have PowerPoint.

MR. MICHAEL KAWCZYNSKI: Dr. Wolfe? Dr. Wolfe, you can't listen to it on the -- Dr. Wolfe?

DR. SIDNEY WOLFE: Yes.

MR. MICHAEL KAWCZYNSKI: Okay. Dr. Wolfe --

DR. SIDNEY WOLFE: Can you hear me with the speakerphone on?

MR. MICHAEL KAWCZYNSKI: No. Yeah. You have to turn your TV off or otherwise we're going to hear the delay. So please turn your TV off or whatever you're listening to.

DR. SIDNEY WOLFE: I will turn it off right now. It's off.

MR. MICHAEL KAWCZYNSKI: All right.

DR. SIDNEY WOLFE: Can you hear me on speakerphone? I'm doing speakerphone now.

MR. MICHAEL KAWCZYNSKI: Yes, we can, sir. Yes, we can.

DR. SIDNEY WOLFE: Can you hear that?

MR. MICHAEL KAWCZYNSKI: Go ahead, sir. Yes, we can. Go ahead, sir.

DR. SIDNEY WOLFE: I'm Dr. Sidney Wolfe, founder, and senior advisor of the Public Citizens Health Research Group. I have no conflicts. With the surging pandemic and interim efficacy and safety results made public two days ago, we now agree with the need for an EUA for Pfizer-BioNTech COVID vaccine. There's an important unresolved conflict though.

If an EUA is granted for widespread use, should the 19,000 participants in the trial who received a placebo be notified of this and be offered a vaccine by Pfizer, clearly encouraging them to stay in the trial. Similarly, should blinded vaccine recipients be told of their status, thereby encouraging

continuation in the trial? What would you wish if you were subjects in the trial?

As status uninformed trial participants, you might otherwise leave the trial to get vaccinated with the Pfizer or any other EUA available vaccine. The unblinding of vaccine providing proposal has important advantages. First, once an EUA's granted, the ethical obligations, as Pfizer says, to both inform all placebo recipients of their status and offer them vaccine within the context of the trial, is met.

Second, by retaining more trial participants than if the trial remains blinded after an EUA, more recipients may be followed afterwards. The originally vaccinated group could be compared with the newly vaccinated group to continually compare rates of new COVID-19 infection with increasing duration of vaccination as well as adverse reactions.

FDA has said that it doesn't consider availability, as you have all heard, of a COVID-19 vaccine under an EUA in and of itself as grounds for

immediately stopping a blinded follow up in an ongoing trial or offering a vaccine to all placebo recipients.

During the October 22nd meeting, during Dr. Doran Fink's presentation, someone asked, "What about the problem of retaining placebo patients post EUA?" And Dr. Fink responded with regards to mitigating the risk of dropout from ongoing clinical trial, "We do share that concern. I don't have any specific remedies to offer at this time. We've asked the vaccine manufacturers to think carefully about how they would ensure clinical trial retention."

Pfizer has stated in a briefing document, "It intends to continue the pivotal Phase 3 study with participants in both the vaccine and placebo groups as originally allocated for as long as possible," emphasize that. "Nevertheless, we have an ethical responsibility to inform all outgoing" -- all ongoing rather -- "study participants the availability and eligibility criteria of the vaccine made available under an EUA."

They would accommodate those trial participants wishing to leave the trial by reviewing which group they are in, but they can receive the vaccine only when practically eligible, depending on the government specified priority group and the available supply. But Pfizer's real preference -- and this is in the briefing documents -- is that such placebo individuals are vaccinated within the study in order that both safety and efficacy data can continue to be collected. We believe this approach will minimize the number of current participants --

MR. MICHAEL KAWCZYNSKI: Time.

DR. SIDNEY WOLFE: -- who withdraw from the study. If you were in the trial, would you prefer being unblinded only if you wished to leave the trial to seek possibly available but needed vaccine? Or being automatically unblinded given Pfizer's vaccine if in the placebo group or happy to find out --

MR. MICHAEL KAWCZYNSKI: You need to wrap it up.

DR. SIDNEY WOLFE: -- to stay in the trial? Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Kim Witczak.

MS. KIM WITCZAK: Yes. Good afternoon. My name is Kim Witczak and I'm speaking on behalf of Woody Matters, a drug safety organization started after the death of my husband due to an undisclosed side effect of antidepressants. We represent the voice of families who live every day with the consequences of the current drug safety system. I am also on the board of directors for U.S.A. Patient Network, and independent patient voice advocating for safe, effective, and accessible medical treatments.

Right now the world is looking for hope so they can get back to normal. Too many lives and livelihoods have been lost. Like many of us, we put blind faith and hope in the system that ultimately failed us. I have several concerns about rushing novel vaccines to market.

The public needs assurances that the FDA's review was thorough and independent. Given the process for reviewing new products usually takes six to ten months. How could the FDA be as rigorous in weeks this time? Is there a process in place if there are dissenting scientific reviews within the Agency? This needs to be available, and FDA scientists need to be protected for whatever their judgment is, and not be political like it has been with many of the past controversies such as antidepressants and suicide has been handled within the Agency.

Transparency is everything. Assuming FDA approval, then all trial data must be released and made public. This also includes the process information like Pfizer's data monitoring committee who determined it was safe. Is it public? If not, it should be. We also need a transparent process for catching safety signals and communicating with the public. It needs to be real-time like we saw in the U.K. yesterday with the allergic reactions and not reported in weeks, months,

years later like history has shown.

Post-market monitoring will be more important than ever. We really don't know what short and long-term harms are given the short duration. Will FDA be staffed to handle the large task of closely monitoring that will be needed? Like MOD, the medical device recording system, which includes patient narratives in the reporting, the FDA needs to do the same for the VAERS. Narratives can help tell a more complete story than just the data without giving away important patient details.

Finally, I have huge concerns with possibly unblinding of placebo participants and giving them the actual vaccine as Pfizer's CEO alluded to be willing to do. If this happens, we lose our control group. In closing I'm directing this comment to the news media.

You have a huge responsibility to dig deeper ask critical questions, and not be just an extension of the manufacturer's PR department. And accept press releases like the Wall Street Journal article did

earlier this week and included a Pfizer-supplied chart showing efficacy by subgroups where blacks had 100 percent efficacy. This should have sounded alarms and begged for additional questions. And then they would have dug deeper and realized there weren't a whole lot of blacks in the trial. Please seek out independent researchers, scientists, and others without political or financial agendas.

Ultimately, the public is the real-world clinical trial. It is one big human experiment. The only ones that have 100 percent immunity in this will be the pharmaceutical companies. They get all the benefits of sales without any of the legal liability should something go wrong. I'd like to thank you for your careful consideration of my comments. I know firsthand the importance of your advisory committee work. Thank you.

DR. PRABHAKARA ATREYA: Okay. The next speaker is Ms. Lynda Dee.

MS. LYNDA DEE: Hi. Thank you. I'm from AIDS

Action Baltimore and the AIDS Treatment Activist Coalition. I have no conflicts of interest. The answer to both Agency questions on COVID-19 prevention and the risk benefit ratio are clearly yes in my opinion. Many of the issues submitted in my written comments have been addressed by the sponsor submission.

One important ethical issue, involving maintaining participants in the placebo arm after EUA, has been discussed. I think it is very reassuring that the sponsor's proposing the placebo participants be permitted to decide whether to remain on the placebo or to receive the vaccine within the study at the appropriate time. The crossover design will hopefully ensure that the study will not crash.

Crossovers are nobody's favorite, but an unblinded crossover is probably much more feasible here. Laypeople have no understanding of the nuances discussed today. Acceptable designs, that will confirm initial EUA data and protect current participants and suspicious future potential participants promoting

public trust, are essential.

I do have a few important remaining concerns. The DART study for pregnant women should be much further along by now. Also, the sponsor is essentially claiming that safety and efficacy have been established across race and ethnicity. The analysis of 3,800 Phase 2/3 participants includes only 0.5 percent Native Americans, 9.3 Black or African Americans and 28 Latinx people. The Native American and Black or African American numbers are especially concerning in these key populations, who are disproportionately affected by and who experience greater adverse COVID-19 related comorbidities and deaths.

While my community appreciates the eventual inclusion of people with HIV, HBV, and HCV per Amendment 6, the mere 120 people with HIV enrolled is abysmal. The sponsor has submitted zero separate data on people with HIV, HBV, and HCV or people over 75. Thus, there is absolutely no data to guide vaccine use in these populations.

This is especially concerning for people with HIV as there's mounting evidence of disparate, adverse coinfection outcomes. VRBPAC should recommend that the sponsor conduct post-EUA research to establish safety and efficacy in significant numbers of people over 75, and people of color and people with HIV, HBV, and HCV, where feasible, without excluding them from any indication.

Finally, I hope we don't begin by lagging behind in the enrollment of people of color in COVID-19 research. I sincerely hope Pfizer will include consumers in its vaccine expert safety subcommittee and will convene community meetings to discuss trial designs, as well vaccine education and accrual and retention issues. This practice has served both the HIV community and sponsors very well over many years of successful and mutually beneficial drug development. Thank you and the FDA for such dedicated service and for the opportunity to comment.

DR. PRABHAKARA ATREYA: Okay. Thank you.

Next speaker is Peter Lurie.

DR. PETER LURIE: Good afternoon. I'm Peter Lurie, president of the non-profit Center for Science in the Public Interest and Associate Commissioner at FDA from 2014 to '17. I have no conflicts of interest to disclose. I would like to thank the FDA for conducting its review in a transparent manner, and for committing to the advisory committee review process particularly under concerted political pressure.

I just want to address two issues today. First, based on the data accrued to date, the Pfizer product demonstrates a striking degree of efficacy in preventing confirmed COVID-19, one that is shared across a variety of demographic, clinical and other subgroups. I agree with the FDA reviewers that there is no evidence of a major safety signal. However, the extent of more minor adverse events is notable. These include injection site reactions, fatigue, headache, all in over 50 percent of subjects, and chills in almost a third. All substantially elevated compared to

rates in the placebo group.

I do not believe that these events should stand between this product and authorization. But I do think the rates of these events are sufficiently elevated to merit open and even-handed discussion with patients. We're already facing significant levels of vaccine hesitancy and, if patients are not forewarned about these adverse events, their word will surely spread rapidly, potentially exacerbating the hesitancy problem. I also welcome FDA's identification of the disproportionate numbers of Bell's Palsy cases, and hypersensitivity-related adverse events observed in the treated group, as matters that should continue to be monitored including in the post-marketing phase.

The second issue relates to trial design now that at least one safe and effective vaccine has been identified. The issues are complex, but we ought to be able to agree on this; no subject who has put their body on the line in a vaccine study should be at a disadvantage in terms of vaccine access as a result of

their participation. Some observers appear to be advocating for extended periods of blinded follow up even after authorization. This position is hard to justify ethically, if it is inconsistent with public health recommendations at the time, particularly with rapidly rising case rates and the reported levels of effectiveness for the Pfizer and Moderna vaccines. So let me propose the following framework, which I think we can all agree on -- at least most of it.

One, subjects should be informed if any vaccine candidate is authorized, not just the one in their trial. Two, like any study subjects, those in vaccine trials should be given the opportunity to leave the trial at any time if they so desire. Three, given the shortages of available product, subjects should be offered vaccination with an authorized vaccine as soon as it is offered to those in their clinical or demographic group in accordance with federal or state guidelines.

Four, those for whom the product is not yet

recommended can continue to be followed in blinded fashion. And five, vaccination is recommended for an individual, a good option is to do so in a blinded crossover manner as described by Dr. Goodman to facilitate blinded follow up for long term safety and efficacy outcomes. I believe that this will facilitate the collection of essential data while honoring the contributions of the tens of thousands of people whose altruistic efforts have brought us to where we are today. Thank you.

DR. PRABHAKARA ATREYA: Okay. Thank you. The next speaker is Andrew Spiegel.

MR. ANDREW SPIEGEL: Yes. Thank you. Thank you for allowing me the opportunity to provide comments on this most important day. My name is Andrew Spiegel, and today I present in my role as Chair of the World Patients Alliance. I have no disclosures.

The World Patients Alliance is a global umbrella organization of nearly 200 patient organizations from 86 countries representing hundreds

of millions of patients across diseases world-wide. My very brief comments today fall into three basic areas, dedication, commitment to science and transparency and innovation.

First, we want to applaud the dedication of the scientists both within the private companies and within the FDA. In the last year, scientists and researchers have fought tirelessly to create a vaccine for the Novel Coronavirus and put it through rigorous processes to ensure its safety and its efficacy. We are comforted in knowing that the FDA will require rigorous post-distribution data monitoring, to continue to ensure any approved vaccines will be safe for the population.

We know that in these unprecedented times the people of America, and the people of the world, deserve to know that their governments are working to eliminate this threat. And we want to make sure that the FDA knows that we will continue to hope that it keeps the patients at the forefront of all of its policy and

approval decisions on these vaccines as well as other medicines. The entire world is watching what the FDA is doing and, as everyone knows, they're relying upon the FDA's commitment to patients.

Last, as the Coronavirus vaccines continue to be approved and used in countries around the world, we must continue the process of innovation. Developing countries need access to innovative medicines now more than ever. In future breakthroughs, the vaccine for COVID could be manufactured as a pill, that would be easily distributed and prescribed in those countries with less access to healthcare professionals around the globe.

I certainly am in agreement with other speakers before me on the issue of ensuring diversity in clinical trials, and ensuring trial members get access to the vaccine, and will not repeat further comments on that. Thanks again to all the stakeholders who have come together in an unprecedented way, during these unprecedented times, to do what would be

unthinkable in the past. On behalf of patients around the globe, we thank you for your hard work and your commitment.

DR. PRABHAKARA ATREYA: Okay. Great. The next speaker is Nissa Shaffi.

MS. NISSA SHAFFI: Good afternoon. I'm Nissa Shaffi and I'm here today on behalf of the National Consumers League. I have no relevant conflicts of interest. We extend our gratitude to the Vaccines and Related Biological Products Advisory Committee for the opportunity to present public comment today on behalf of consumers, regarding the deployment of an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine.

Firstly, we want the thank the Food and Drug Administration, Centers for Disease Control and Prevention and other public health agencies for their demonstrated commitment to fostering public trust throughout the COVID-19 vaccine development and approval process. As consumer advocates, we have been

encouraged by the honesty, transparency and access afforded to the public during this critical time. To that point, there has never been a more critical time for consumers to have confidence in the FDA. The Agency has undergone scrutiny from the scientific community for prematurely issuing EUAs for COVID-19 therapeutics.

NCL is aware that developing a vaccine for COVID-19 is a time-sensitive priority and appreciate that the FDA recognized that an EUA is not intended to replace long-term, randomized clinical trials data associated with full FDA approval. We look forward to continuing guidance around the vaccine as the trial continues to collect safety and efficacy data two years post-release. We have great trust in the FDA's rigorous vaccine approval process and call on the Agency to perform ongoing post-market surveillance to ensure the vaccine's ongoing safety and efficacy.

Post-market surveillance performed in the U.K. yielded that the vaccine is unsafe for individuals with

severe allergies. We call on the FDA to heed these warnings and to continue to sustain its robust inter-agency collaboration towards the evaluation, approval, and distribution of the COVID-19 vaccine. Consumers will rely on ongoing guidance from public health agencies regarding any potential adverse events from the vaccine.

Additionally, ensuring innovative vaccine delivery methods, such as including oral or nasal options, could address geographic access issues as well as adequately consider diverse health needs increasing overall uptake. We welcome efforts to ensure diversity in the clinical trials for the COVID-19 vaccine, and NCL requests that the FDA continue to prioritize vaccine clinical trial data that reflects diversity as people of color will need to have confidence in the vaccine's efficacy in their communities. This will impact overall uptake of the vaccine.

The development of a COVID-19 vaccine in such record time has been a miraculous feat made possible

through robust collaboration between private and public entities. NCL will continue to support the FDA and CDC in its efforts to release a COVID-19 vaccine safety and expeditiously. Thank you to the committee for your consideration for our views on this important public health issue.

DR. PRABHAKARA ATREYA: Okay. Thank you. The next speaker is Julie Omohundro.

MS. JULIE OMOHUNDRO: Good afternoon. I'm Julie Omohundro, unaware of any conflicts of interest. I will cover two points in the comments I submitted and leave you to read through those as you please. They were submitted under the banner of the Regulatory Watch Cat and easily identified by a cute, black cat.

I start with a question. Does the EUA violate Article 37 of the Declaration of Helsinki, which states that unproven interventions should not be used in medical practice without informed consent? This led to the question as to whether authorized products are proven or unproven, and whether their use is medical

practice or research. Eventually, I concluded that EUA lies in an ethical gray area, falling along several continuums.

I consider a few such continuums and ethical questions that they might raise. I also looked at ethical standards in 21 CFR, the Belmont Report, and the AMA Code of Medical Ethics. Finally, I considered Section 564 of the Food Drug and Cosmetic Act and the current status of both informed and consent for EUA products.

Section 564 requires informing patients that the product has been authorized for emergency use. The problem is that patients don't know what the means. Currently, providers and patients are provided with product factsheets, all apparently based on the same template. The language addressing the product has been authorized for emergency use comes directly from Section 564, which was not written to inform patients of anything. It is not in language understandable to patients nor to providers.

Currently, there's much confusion among manufacturers, providers, and patients regarding the regulatory status of authorized products and what can reasonably be expected of their safety and effectiveness. It is the latter that patients and providers need to understand and where the factsheets fall far short. If individuals with the appropriate expertise could evaluate concepts such as proven versus unproven, medical practice versus research, as they apply to EUA and as points along a continuum, this could provide a rational framework for addressing ethical concerns that have emerged with the EUA, as well as the appropriate regulatory oversight and the appropriate use of clinical data generated from the use of an EUA product.

I don't think this type of evaluation is suited for Warp-Speed. Therefore, in the interim, I ask the committee to consider that the risks presented by the EUA include not only ethical risk but also loss of public trust, a serious risk for any public health

program. If issues emerge with the use of a new medical product, patients and providers rarely go back to, "What was I told?"

I hope FDA will give serious consideration to moving forward with any COVID-19 vaccine initially under expanded access, rather than EUA, to assure adequate ethical oversight, informed consent, and early access to a vaccine by the populations that most urgently need it. In addition, for the love of Harvey Wiley and Jenna Sock (phonetic), please, please, have an IRB take a look at the template for the patient factsheet. Thank you.

DR. PRABHAKARA ATREYA: Okay. Great. The next speaker is Dru West.

DR. DRU WEST: Thank you. Thank you for this opportunity to comment. My name is Dru West and I'm the President of the U.S.A. Patient Network. Our organization is composed of many patients and family members who have been affected by pharmaceutical and medical devices that promised hope but left our members

or family members harmed with lifelong side effects and sometimes death. We have no conflicts of interest to report as we are a completely independent voice for patients and their families.

Our concerns are based on lived experience. Every person receiving a COVID vaccine needs to know the answers to basic questions such as, will this vaccine prevent the most serious symptoms or the spread of the disease? What side effects or problems might occur immediately, mid-term and long-term? And how long will this vaccine protection last?

It's our opinion that at this time there are too many unanswered questions regarding the safety and efficacy to release the vaccine. The release of these vaccines will make participants unwitting subjects in a seemingly uncontrolled clinical trial. That said, we recognize the tremendous pressure being placed on the FDA to act. Therefore, in the absence of reasonable assurances of safety and efficacy, we ask that the release of this vaccine be done cautiously and with

thoughtfulness for the health and well-being of the recipients. We ask that you proceed slowly with release of these vaccines on a voluntary basis until full conclusion of blinded Phase 3 clinical trials.

We ask that you exclude populations that have not been studied or thoroughly studied, such as, pregnant women, frail elderly persons and severely immunocompromised persons, among others. We also ask that you continue, or expand existing or new clinical trials, to include groups of people who have not yet been included in any clinical trial to truly determine safety and efficacy. We ask that you monitor the vaccine recipients long term over time, by collecting and analyzing data to identify the real world safety and adverse response results.

This includes giving clear instructions and encouragement to vaccine recipients on what, where and how to report adverse response events not just reporting to their doctors. We ask that you give complete, informed consent information that includes

full disclosure of the ingredients in the vaccines, all possible adverse responses as well a statement, in plain language, that the current safety and efficacy information is incomplete, and that the vaccines have not yet been studied for safety and effectiveness for everyone or studied for adverse responses or effectiveness over time. We thank you for hearing our concerns.

DR. PRABHAKARA ATREYA: Okay. Great. Thank you. The next speaker is Sarah Christopherson.

MS. SARAH 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 non-profit advocacy organization that has been bringing the voices of women to the FDA for 45 years. We are supported by our members and do not accept financial support from drug or device makers. And I have no conflicts of interest to disclose.

We applaud the FDA for their diligent work during this public health emergency on desperately

needed vaccines including, yes, over Thanksgiving. However, we do have serious concerns that moving forward with an Emergency Use Authorization, based on so little data for so many of the communities that have been hardest hit by this virus, will do little to assuage legitimate concerns in those communities about taking the vaccine.

As we heard this morning, CDC data indicates that Black and Indigenous people living in the U.S. are roughly four times more likely to be hospitalized from COVID-19 and roughly three times more likely to die from the virus than their white counterparts. And as we heard at the October 22nd meeting, members of those communities have also expressed a really strong interest in knowing that the vaccine will work in people like them. Without those assurances, black Americans have expressed high rates of COVID vaccine hesitation, and for good reason.

Black Americans don't have to look back to the last century or to the infamous Tuskegee study to see

examples of the medical system undervaluing them. And many black and Indigenous people have had multiple discriminatory and negative experiences with the medical system in their own lives. Pew Research found a clear link between confidence in the regulatory process that you all are pursuing and American's willingness to get the vaccine.

Before authorization is granted, affected communities need to have confidence that the vaccine is safe and effective for people like them. The efficacy data submitted to this panel includes fewer than 2,000 black or African American vaccine recipients, and just 131 American Indian or Alaskan Native recipients, not counting the placebo-control population. The safety data included just 206 black seniors, 65 or older, and just 131 American Indian or Alaska Native people of any age.

If this advisory committee votes to recommend authorization based on this data, FDA must ensure robust tracking and bold public transparency once the

vaccine is taken. Otherwise, the near-term side effects of the vaccine, which have been mentioned earlier, such as fever, chills, pain, fatigue, all of which could be really quite alarming to the public not expecting it, could further fuel distrust among communities that have been given little reason to trust this process. Thank you.

DR. PRABHAKARA ATREYA: Okay. Thank you. The next speaker is Vicky Pebsworth.

DR. VICKY PEBSWORTH: My name is Dr. Vicky Pebsworth. I have no financial conflicts. I'm a public health scientist and nurse who has served as consumer representative on VRBPAC. I am the Volunteer Director of Research and Patient Safety for the National Vaccine Information Center and the mother of a child injured by his 15-month well-baby shots in 1998.

The normal U.S. vaccine development, testing, and licensing process takes 10 to 20 years. When accelerated and when population studies are not large enough, or do not closely match those targeted to be

vaccinated, the public assumes unknown and potentially increased risks. Under the Emergency Use Authorization, COVID-19 vaccines can be approved but remain experimental and unlicensed while manufacturers are shielded from liability if the vaccines cause harm.

The EUA factsheet prepared for the public must be transparent, and fully disclose known and unknown risks of the Pfizer-BioNTech COVID-19 vaccine, to guarantee fully informed medical decision making and to ensure public confidence. Specifically, the EUA factsheet should disclose whether the vaccine is at least 94 percent effective in preventing SARS-CoV-2 infection and transmission, or only prevents severe COVID-19 disease, hospitalization, and death.

Whether there is evidence for antibody acquired and T Cell mediated immunity, and how long it lasts. Whether there is a risk of enhanced COVID-19 disease when vaccine recipients are exposed to the SARS-CoV-2 virus or have previously received flu shots or other vaccines. Whether there is evidence for

immediate and/or delayed serious vaccine reactions and poor health outcomes, especially in those who have already had COVID-19 disease, have severe allergies, experience severe reactions to previous vaccinations or are chronically ill.

The EUA factsheet must clearly identify populations excluded from clinical trials. Over 40 criteria excluded certain people from some trials, including pregnant women and children, those with high blood pressure, obesity, diabetes, asthma, heart, lung and kidney disease, neural and immune problems, and those using certain medications or with a history of vaccine reactions or over age 85. Will the vaccine be safe and effective for them?

The EUA factsheet must clearly list all vaccine ingredients and disclose that an aborted fetal cell line was used to test the vaccine, as reported in a September 2020 paper published by 61 Pfizer and BioNTech scientists. By law, the EUA factsheet must state that the consumer has the option to accept or

refuse the vaccine.

It is the position of the National Vaccine Information Center that using coercion and sanctions to persuade adults to take an experimental vaccine, or give it to their children, is unethical and unlawful. Thank you for your consideration.

DR. PRABHAKARA ATREYA: Okay. Thank you. The next speaker is Martha Nolan.

MS. MARTHA NOLAN: Good afternoon. Thank you for the opportunity to speak with you today. I am Martha Nolan, Senior Policy Advisor at Healthy Women. Healthy Women is the nation's leading non-profit health organization representing more than 18 million women. We provide consumers and healthcare providers with accurate, evidence-based information about diseases and conditions, innovations in research and science and changes in policy that affects women's access to treatment and care.

I'd like to first thank you for the thoughtful and important work you are doing today and all that

you've been doing throughout the pandemic. The discussion today is truly historic, and I commend all of you for your leadership and careful consideration of the data that is before you. Whether today or in the future as COVID-19 vaccines are authorized by this body, I know that we are all cognizant of the challenges that lie ahead in terms of public trust.

The science being presented today is truly remarkable, and the transparency of this meeting and the sharing of information from all of the companies as they work to develop COVID-19 vaccine candidates is the first step in bolstering public trust. As you're aware, recent surveys among the general public, but also somewhat surprising among healthcare workers reveal concerns around the safety of COVID vaccines and many myths and misconceptions. When you look at communities of color, the level of skepticisms are even higher.

All of us who work in public health must look to address this issue and working together will be

particularly critical. That is why Healthy Women is co-leading an effort with more than 60 other public health organizations representing patients, caregivers and families, diverse communities, healthcare workers, older Americans, veterans, front line workers and scientists, to work together to alleviate the concerns and hesitancy associated with the COVID vaccines. The COVID-19 Vaccine Education and Equities Project's mission is to educate and raise awareness of the importance of the COVID-19 vaccination for public health, the economy, and the broader society, as well leading the conversation to ensure equitable access to authorized and approved vaccinations.

The key to getting our lives back to normal here in the U.S. and across the globe hinge on the success of COVID-19 vaccinations. But we also know that vaccines are only as effective if they are trusted and taken by the majority of the population. We look forward to continuing our work to help build that trust, and thank all of you, again, for the work you're

doing to ensure that the coming vaccines are safe and effective. Thank you.

DR. PRABHAKARA ATREYA: Okay. Great. Thank you must. The next speaker is Mitchell Warren.

MR. MITCHELL WARREN: Thank you so much. My name is Mitchell Warren and I'm the Executive Director of AVAC, a non-profit organization founded in 1995 to accelerate the ethical development and global delivery of HIV vaccines and other new prevention options. And in March we joined with several organizations to establish the Global COVID Advocates Advisory Board. I have no conflicts to declare and we accept no funding from pharmaceutical companies.

AVAC enthusiastically welcomes the safety and efficacy data of the Pfizer-BioNTech mRNA vaccine candidate being presented today. This is terrific news to be sharing on a triumph of science and partnership. While the data to us should clearly warrant an EUA, they also require the maximization of additional data collection to address a number of remaining questions

and issues that need to be addressed.

One, the critical importance of distinguishing between an EUA and licensure under a BLA, and for you all to help ensure that continued data collection and a clearly articulated pathway and timeline for a BLA is provided. Two, there continues enormous need for the inclusion of diverse populations in COVID vaccine trials generally. And the data under review today provide limited information about the safety and efficacy data in diverse populations, including people living with HIV, other immuno-compromised people and those who are pregnant and breastfeeding. It is essential that specific requirements and timelines be articulated so that these key populations are not left behind. And I want to underscore my colleague, Linda Dee's, earlier comments on the critical importance of equity, diversity and inclusion in research and review.

Three, with only two months of follow up data as per EUA guidance, it is essential the future BLAs include at least six months of follow up. Therefore,

continued blinded follow up of the trial is warranted while recognizing that some trial participants will want to exercise their rights to leave the trial and, if from the placebo group, seek vaccination.

If an EUA is granted, it will be urgent for the FDA and the companies to rapidly develop clear information including an explicit re-consent process outline the benefits, risks, and rights of maintaining in the blinded trial for both public and personal benefit. And strongly encourage the committee to endorse the deferred blinded crossover design proposed by NIAD and presented earlier. In addition, we encourage the FDA to urgently issue guidance to other developers who will need to address this issue.

Fourth, perhaps the biggest unknowns remain the durability of vaccine efficacy and whether the vaccine prevents asymptomatic disease and will limit transmission. A clear plan to collect and communicate information to inform answers from within the ongoing trial, as well as in the design of additional trials,

is essential and should be clearly articulated when any EUA is announced. And should be strategically linked to other vaccine developers to jointly identify correlates, bridge data to other populations and platforms, and track use. As we've seen repeatedly in this pandemic and throughout HIV, clear evidence-based information is key.

In conclusion, AVAC applauds this mRNA vaccine and both this VRBPAC and FDA for its commitment towards transparency, independence and evidence-based scientific decision making. This process is not just about authorization or approval, it is a beacon of independent review and transparency that will help to foster the trust necessary to rebuild confidence in vaccines, in science and in our public institutions.

Thank you for what you're doing today and throughout this process. And thank you for the opportunity present and looking forward to continued engagement with scientific and regulatory processes that move with speed of trust.

DR. PRABHAKARA ATREYA: Okay. Great. Thank you. I think we are almost come to the closure. We tried the last person requested and then we're unable to reach her. I think we can conclude because we already are past 10 minutes past the actual time for the next presentation. But before we go to sponsor presentations, the Director of the Center for Biologics, Dr. Peter Marks, would like to make a few comments. Then we'll go to sponsor presentation. Thank you. Dr. Marks, you're on.

DR. PETER W. MARKS: Thanks very much Prabha. I just want to take a moment here to offer some thanks to various people. First of all, thanks to anyone from the public who's tuning in today. I think having this as a transparent process is very important as one of the steps we're taking to try to enhance vaccine confidence across the country.

I also want to take a moment to thank all of the advisory committee members and the speakers today. They're contributions are immense, and we'll look

forward to their discussion later on today. It's also very important for me to take a moment to thank a group of people at FDA; that have put an incredible amount of effort into this advisory committee meeting while they're simultaneously getting ready for another advisory committee meeting and taking care of many other vaccines in various stages of development.

The amount of work that has been put into this, by those just setting up these meetings, is tremendous. And I'd like the thank Prabha and all of the advisory committee staff, but also an incredible debt of gratitude to all of our reviewers in various offices and especially in our Office of Vaccine Research and Review. The leadership and the staff in that office have worked tirelessly throughout the past weeks and months to get to this point, and that included working diligently over this past holiday when they could have been spending time with their families.

So we're very, very grateful for all of the work and grateful to all of you. So with that, I want

to let this proceeding move on since it's going to be a long day anyway. But thank you very much.

DR. PRABHAKARA ATREYA: Thank you, Dr. Marks. Now, Dr. Monto, back to you to take on from this point on for the next presentation with the sponsors.

SPONSOR PRESENTATION

DR. ARNOLD MONTO: Right. Next, we have the sponsor presentations. The moderator is Kathrin Jansen, Senior Vice President and Head of Vaccine Research and Development at Pfizer, and William Gruber, Senior Vice President of Vaccine Clinical Research and Development at Pfizer. You're on.

DR. KATHRIN JANSEN: Good afternoon members of the committee, FDA, and ladies and gentlemen in the audience. It is a real pleasure to be here today. I'm Dr. Kathrin Jansen and I'm a Senior Vice President and head of Vaccine Research and Development for Pfizer. I would like to thank the FDA for organizing the VRBPAC,

and the VRBPAC chair and members for their time. Pfizer and our partner, BioNTech, are pleased to be here today to discuss our candidate mRNA COVID-19 vaccine program in the context of requesting an Emergency Use Authorization.

Our presentation today will follow this agenda; after I give a brief introduction, Dr. William Gruber, Senior Vice President Vaccine Clinical Research and Development, will review the development program for our vaccine including non-clinical, clinical safety and clinical efficacy data. After this, I will come back to review the benefits-risks and provide conclusions for our presentation.

We are also pleased to have a principal investigator with us to answer any study-related questions. Dr. Stephen Thomas, who is Professor of Medicine and Microbiology and Immunology, Chief Division of Infectious Diseases, and Director Institute for Global Health and Translational Sciences, from the State University of New York Upstate Medical

University.

Our COVID-19 mRNA vaccine called BNT162b2 has been developed for the following indications: prevention of COVID-19 in individuals 16 years of age and older. The dose level is 30 micrograms with two doses given 21 days apart. The vaccine presentation is a five dose, multi-dose vial that is preservative free and stored frozen between -80 and -60 degrees Celsius until use. Since the beginning of the year, we have been facing a devastating situation with COVID-19, the disease caused by the new Coronavirus, SARS-CoV-2.

Tens of millions of people have been infected globally and over 1.5 million people have already died. No one is safe from this disease and certain groups, such as healthcare workers and first responders, the elderly and people with underlying diseases, are at particularly high risk. It is now becoming very clear, particularly with the recent increasing rates of COVID-19 globally and in the United States as discussed earlier by Dr. Hall, that we need a safe and

efficacious vaccine to stem this devastating pandemic while also deploying other prevention strategies such as infection control, including mask wearing and social distancing.

SARS-CoV-2, the virus that causes COVID-19, is a new beta-Coronavirus that emerged late in 2019 in China. Shown in red are the Coronavirus glycoprotein spikes called S for short. The spike protein is an important vaccine target or antigen as it mediates first the specific binding of the virus to the H2 host cell receptor and then the fusion of the viral envelope with the host cell membrane. By these actions, the virus enters into human cells where it replicates then spreads to other people and often causing illness in the infected individual.

Data available from other Coronaviruses, such as SARS and MERS, have established that antibodies 2S can stop the binding of the virus to cells and prevent the virus infection of the human cell. So we chose the S protein as our vaccine antigen. Specifically, we

chose a form of the S protein that was engineered to lock it in the profusion confirmation which is thought to be optimal for eliciting functional virus-neutralizing antibodies.

We chose BioNTech's mRNA vaccine platform for a number of reasons and given BioNTech's long experience with messenger RNA vaccines in the oncology space. mRNA vaccines are produced by self-reproduction processes using chemically highly-defined vaccine components, RNA, and lipid. mRNA vaccines can induce broad immune responses well-suited to address a new pathogen in a situation where there's no or limited knowledge of what correlates with protection.

The mRNA vaccine platform lacks unwanted viral or vaccine platform antigens that may lower a vaccine-induced immune response. As a consequence, mRNA vaccines can be boosted repeatedly, an important consideration when persistence of vaccine immunity is not yet known. Given that mRNA vaccines are essentially synthesized, they can be developed and

scaled up quickly. A clear advantage over cell-based production processes when developing a vaccine in a pandemic setting.

So how does an mRNA vaccine work? We have a deep scientific understanding of how such vaccines work. The mRNA code, that means harbors information for the vaccine antigen which is a form of the S protein. The mRNA is stabilized through formulation with lipids to form what we call lipid nanoparticles, or LNP. The LNP formulation is further optimized to allow efficient entry of the LNPs into human cells.

This LNP is also optimized to be able to enter antigen-presenting cells that are efficient at simulating a broad immune response which we desired given that we did not know, and still do not know, which response best correlates with protection. Inside the cell, the mRNA is released from the LNP. Just like any other messenger RNA in the cell, the mRNA from the vaccine can direct the synthesis of a protein by the cell's own production machinery.

And since our vaccine codes a form of the SARS-CoV-2 spike protein, that protein is also produced. Once produced, the whole S protein and its smaller fragments are presented to the human immune system that recognizes the protein as foreign resulting in simulation of T-Helper Cells or CD4 T Cells that activate other T Cells and antibody producing B-Cells. The antibodies can bind to the S protein on our SARS-CoV-2 and neutralize the virus, which means the virus is no longer capable of infecting a cell.

Also produced are CD8 T Cells that can eliminate virally-infected cells. An important feature of mRNA vaccines is that they stimulate affected B-Cell and T Cell memory responses. The ensures longer term protection from viral infection and disease.

An additional advantage of the mRNA platform is that the vaccine induces a Th 1-biased, CD4-positive T Cell response that is linked to protection from viruses and thus minimizes a theoretical risk of vaccine-enhanced disease. The Th 1-biased response is

characterized by secretion of cytokines involved in fighting a viral infection such as interferon gamma and IL-2. So in a nutshell, the immune responses induced by the mRNA vaccine are similar to what you may get in response to a viral infection. But of course, the mRNA vaccine is non-infectious and cannot cause disease.

When we started our COVID-19 vaccine partnership with BioNTech, we had the choice of a number of different mRNA vaccine candidates, different flavors of the mRNA, and different forms of the Spike protein. Given the enormity of our mission, clinical data were important to us in deciding on the right candidate for a COVID-19 vaccine. So we evaluated not just one but four different candidates, in Phase 1, to be able to make real time scientific decisions to select the best candidates based on the following major selection criteria.

With regard to safety, we were looking for the most favorable safety and tolerability profile in both younger and older adults. With regard to

immunogenicity, we were looking for the broadest antiviral immune responses most likely associated with efficacy. And with regards to a rapid pandemic response, we were looking for the candidate that could be developed and produced most efficiently. Using these criteria, we selected BNT162b2 which contains a modified RNA that expresses a code on optimized, full-length, pre-fusion stabilized Spike protein of SARS-CoV-2.

The top priorities for vaccine development in general and for a COVID-19 vaccine, in particular, are as follows: we must demonstrate that the vaccine is highly effective, meaning that it can help prevent COVID-19 in at least the majority of vaccinated people. We must demonstrate that the vaccine is safe with a robust safety dataset generated in a very large, pivotal efficacy study. And we also must demonstrate that we can consistently manufacture the vaccine to the highest standards.

Throughout 2020 we have been asked often, how

can this be done in a year or less when the process normally takes many years? Well, vaccine development or anything else in a pandemic setting is not normal. It requires a completely different way of thinking and a strategy of parallel versus sequential R&D.

Instead of waiting for pre-clinical and clinical data to emerge, substantial efforts and resources were poured into process development and manufacturing scale-up well before any clinical data were available. This has been an unprecedented investment early in development. In planning clinical development, we worked with the FDA and other regulators on a seamless trial which collapsed Phases 1, 2, and 3 clinical development also in an unprecedented way, with close to real time communications and decision making, without ever stopping the trial.

We are grateful to FDA and other regulatory agencies who have lent us their enormous support to work on these seamless development timelines. With

substantial work on the mRNA platforms already done at BioNTech, we were able to quickly start clinical development and advance to Phase 2/3 start at the end of July this year. And we have support from CDC to provide real data on regional SARS-CoV-2 and COVID-19 attack rates, in the United States, to optimize our selection of trial size.

Last but certainly not least, was a dedication of investigators and site staff as well as the motivation of tens of thousands of trial participants. We were able to enroll over 40,000 participants in a record six weeks, give them each two doses of vaccines, and ensure their safety while conducting the trial with strict compliance and uncompromising quality.

And now, let me introduce for you the clear and compelling data package you will hear about today that we believe satisfy the FDA guidance for COVID-19 vaccine's Emergency Use Authorization. We have submitted all of the information required to meet the EUA guidance and you will hear about them this morning.

As for manufacturing data, FDA has reviewed the C&C data submitted to date for our vaccine and has determined that the C&C information is adequate to ensure the vaccine's quality and consistency for authorization of the product under an EUA. And now, Dr. Bill Gruber will discuss the non-clinical and clinical datasets with you as well as our future plans.

DR. WILLIAM GRUBER: Thank you, Kathrin. It's my pleasure to share with you today the development program for our vaccine candidate BNT162b2. I'm going to begin with a very brief summary of the non-clinical data that encouraged us to move forward into the clinic. This includes both toxicity studies as well as a study looking at a challenge study in Rhesus-Macaques. These studies are described in the briefing documents.

Two toxicity studies in rats, including the BNT162b2 vaccine construct, were completed with no safety concerns. Development and reproductive toxicity studies are ongoing with preliminary results available

by mid-December. In a SARS-CoV-2 Rhesus challenge model, the BNT162b2 construct provided complete protection in the lungs as determined by nucleic acid amplification testing for SARS-CoV-2 and bronchoalveolar lavage fluid. This information is now published. And importantly, there was no radiologic or histopathologic evidence of vaccine-elicited disease enhancement.

Despite limitations of animal models, these findings anticipated results in our Phase 3 clinical trial in which there is no evidence of enhanced disease. These results were encouraging, satisfied FDA guidance criteria, and permitted progression of human clinical trials. I'm now going to share with you the clinical safety, immunogenicity, and efficacy data from our overall clinical development program.

First, I will cover safety and immune response from the German and U.S. studies and then cover aspects of the Phase 2/3 trial finishings with the safety and efficacy results. So let's begin with the two Phase 1

studies. The German Phase 1 dose-ranging study was conducted in individuals 18 to 55 years of age. 12 subjects received the active BNT162b2 vaccine for each dose level cohort. This study evaluated safety, binding, and neutralizing antibody responses, as well as cell-mediated immune response to look for the potential for Th 1-biased, CD4, and CD8 T Cell responses.

The U.S. study is a seamless study where we have a Phase 1 portion that moved into Phase 2 and then Phase 3. For the Phase 1 dose-ranging portion, we included 18 to 55 and 65 to 85-year-old individuals. Twelve of whom received vaccine and 3 received placebo per dose-level cohort. We looked at safety and immunogenicity with both binding and neutralizing antibody responses and followed reactogenicity by electronic diary.

These individuals will continue to be followed for a full two years after the second dose. The results from the Phase 1 experience have now been

published and you have details in your briefing documents.

I'll just summarize for you briefly the reactogenicity from Phase 1. Mild to moderate injection site pain was observed frequently and was consistent with local reactions observed with other commonly licensed and recommended adult vaccines. Fever and chills along with other systemic manifestations were observed. Reactogenicity was generally higher after dose two than dose one, and reactogenicity events after each dose of the vaccine in older adults were milder and less frequent than those observed in younger adults.

Now I'd like to summarize for you the antibody responses in Phase 1 to two 30 microgram doses of the chosen BNT162b2 vaccine, focusing on the neutralizing antibody titers from the U.S. based trials. These results have been published in a peer review journal and are described in your briefing document.

By day 28, or seven days after the second 30

microgram dose, through 50 percent neutralizing antibody responses are observed. GMTs are shown at the top of each column. Antibody responses are well maintained, out to day 52, approximately one month after dose two, in both this younger 18 to 55 years of age group and the older 65 to 85 years of age group. GMTs are again shown at the top of each column. The GMTs in vaccinated participants ranged from 1.5 to 3.8-fold higher than the virus neutralizing GMT of 94, observed in a panel of 38 convalescent sera labeled HCS.

So this was very encouraging to us, that we were achieving a functional antibody response that could be associated with protection. It was also very important for us to examine cell-mediated immune response to be confident that we were getting a Th 1-biased CD4 and strong CD8 T Cell response.

These are data from the German trial. This first panel shows gamma interferon intracellular cytokine analysis data. We see a substantial increase

in gamma interferon, very consistent with Th 1, and at levels above responses following natural infection labeled HC. If you look at the middle panel, you can see a relatively higher proportion of S specific CD4 cells expressing gamma interferon, IL-2, or both, compared to a lower proportion expressing IL-4.

So once again, this emphasizes a Th 1-biased that could be associated with protection. And likewise, not only is it important to demonstrate the CD4 responses and the concomitant potential for inducing memory, it was important to demonstrate CD8 T Cell response indicating potential for virus killing of infected cells. And in the right-hand panel, you see a robust CD8 T Cell response that exceeds responses observed from natural infection, again labeled HC.

So on the basis of promising neutralizing antibody response, Th 1-biased, CD4 response as well as the robust CD8 immune response, we were encouraged to move into the Phase 2/3 portion of the study with the BNT162b2 vaccine construct.

Outlined here for you, at a very high level, are the fundamental elements of the trial where our goal is to enroll approximately 44,000 healthy subjects. Stable, chronic disease is allowed because we find it important to make sure that those individuals with underlying diseases are included. They stand to have the greatest benefit from a vaccine because of their high morbidity associated with COVID-19. We also have included individuals with stable HIV, Hepatitis B, and Hepatitis C virus infections.

At least 40 percent of participants are 56 years of age or older. This is important because we recognize that this population is also particularly vulnerable to severe disease. We also recognized the importance of conducting the study in people of color; so we have adopted an approach that assures a diverse racial and ethnicity profile, including Black and African American populations, Asians, and Hispanic/Latinx populations. We've excluded immunocompromised individuals because it's yet to be

determined if different dosing might be required in this population. And as you'll see later, we plan to evaluate those populations in future studies.

So here are the demographics displayed for the full population data (audio skip) on over 43,000 subjects as of November the 14th, with good representation of gender, race, ethnicity and age, with even splits between vaccine and placebo recipients. The age breakdown is highlighted to show the different age groups above and below 55 years old, and in the older 65 and above age group. Note that over 9,000, or 20.9 percent of the 43,000 participants, were over 65 years of age.

So now let me share with you the safety data from our Phase 2/3 portion of the clinical trial. I wanted to highlight something familiar to members of the VRBPAC committee. We have ongoing safety reviews by an independent data monitoring committee of unblinded safety data. And in fact, these are occurring weekly. This makes sense in the context of a

rapidly enrolling trial with this new vaccine candidate.

The DMC consists of four adults or pediatric infectious disease experts and one statistician, all with expertise in assessing vaccine safety, immune response, and efficacy. And the DMC, as recently as this past week, has identified no safety concerns during the duration of the clinical trial and has recommended that the study continue as planned at all of their safety reviews.

This figure summarizes the safety database populations submitted to the FDA for this review. Starting at the bottom, there are over 43,000 study participants with safety data collected in the trial as of the data cutoff on November the 14th. Moving up the figure, nearly 38,000 of these represent a subset with median safety follow up time of two months post dose two, meeting FDA guidance.

This means that there are over 19,000 participants for whom safety follow up data is

available for at least two months, post dose two, shown in the second bar from the top. Of the total safety population there are over 8,000 subjects, shown at the top, from whom seven days of solicited local and systemic reactions were obtained by electronic diary.

Shown here is a schematic of how safety of subjects was monitored. On the left-hand side at the top, vaccination of doses were given 21 days apart. The first dose of vaccine was followed by very intense active surveillance for potential COVID-19 symptoms that would trigger a telehealth or in person visit and nasal swab. This was done both as a safety measure as well as to evaluate efficacy.

Individuals could either be swabbed at the investigative site or obtain a self-swab. We were very intent, of course, on otherwise tracking safety comprehensively, and you can see at the bottom left of the slide that we used an electronic diary to address common reactions seen after vaccine administration, encompassing at least 6,000 subjects and at least 500

in each of the countries that are included in the trial.

We also captured non-serious adverse events one month post dose two. We will actively collect serious adverse events for at least six months post dose two, and deaths and related SAEs after the end of the trial at two years after the second dose. So now let me share with you electronic diary data related to local adverse events.

This represents data that were captured over seven days after dose one and dose two in 16 to 55 and 56 to 85-year-olds. I think you can quickly appreciate looking at the two panels which represent dose one and dose two, that for redness, swelling and pain at the injection site, the type of local reactions are very consistent to those seen with commonly licensed and recommended vaccines with very little redness or swelling. Pain was largely mild to moderate in severity. No grade four local reactions were observed. Again, a very satisfactory safety profile as far as

local reactions.

We also, of course, used the electronic diary to look at systemic events. The orientation of this slide is different in that we are looking first at events seven days after dose one. And those who received the vaccine on the top panel compared to those who received placebo on the bottom.

Looking at both the 16 to 55-year-olds, as well as the 56 to 85-year-olds, you can see that the reactions fall within a tolerable range compared to other adult vaccines. I would highlight fever and chills because these appear to be the most discriminating, as you can see, compared to placebo. But both were within an acceptable range.

Now we are looking at systemic events seven days after dose two. And you can see a somewhat higher incidence of fever and chills as well as other systemic manifestations compared to placebo. The only grade three or severe solicited adverse event, greater than or equal to 2 percent in frequency after the first or

second dose, were fatigue at 3.8 percent and headaches at 2.0 percent following dose two.

One vaccine recipient reported a fever of 41.2 degrees Centigrade only on day two, after dose two, and reported no fevers for all other reporting days. One vaccine recipient reported a fever of 40.7 degrees, on day four after dose one, with no fever at the end of the seven day reporting period. Otherwise, no grade four systemic reactions were observed. There was a difference between younger individuals and older individuals. Younger individuals tended to have more reactions. But in all age groups the vaccine was well tolerated and the reactions were within an acceptable range.

If we consider how these events peak and declined over the seven day post dose two period, in the BNT162b2 group, it can be seen that the duration is short lived. Participants are vaccinated on day one. Fever, the left-most dark blue bar, typically appears on the day after vaccination and lasts only a single

day. Otherwise, systemic events shown as the other colored bars peak at day two then rapidly decline over the next two days in both age groups.

We captured spontaneously-reported adverse events by System Organ Class in the nearly 38,000 subjects subset, for which median safety follow up was two months after dose two. This slide shows adverse events by System Organ Class occurring in one percent or more of the study population. More details are included in your briefing document.

The most common adverse events observed were general disorders and administration of site conditions. As shown in the footnotes, the top four classes of unsolicited reactions in this nearly 38,0000 participant dataset, mirror the common reactions captured by electronic diary in the 8,000 participant subset previously described. For example, these include reports of injection pain, fever, myalgia. For nervous disorders, the highest proportion is headache. For GI disorders, not diarrhea and vomiting.

When we exclude those terms reflecting local reactions and systemic events typically occurring within seven days of vaccination, we see a more even split of adverse events between the active vaccine and placebo, apart from general disorders and administration site conditions where the predominant remaining event is unspecified pain in the vaccine group, 2.4 percent versus 0.2 percent. In general, adverse events by System Organ Class are infrequent and within range of such reactions reported after other licensed vaccines.

Rounding out this part of the safety reviews, serious adverse events shown here by System Organ Class are consistent with what we typically see in populations that not only include 40 percent of individuals being older than 55, but over 50 percent of the population being obese and/or having at least one underlying comorbidity. SAEs have been balanced between vaccine and placebo recipients. These include observed, serious adverse events of special interest

designated by the CDC, which are few in number and comparable between vaccine and placebo recipients.

A total of six deaths have occurred in this population with four of these in the placebo group. None of these have been considered related by the investigators. Further description of these deaths and the full safety data available, as of November the 14th, are included in your briefing documents.

So in summary, the tolerability and safety profile of the BNT162b2 vaccine, at 30 micrograms, administered in a two dose regimen 21 days apart is favorable, and no clinically significant safety findings other than mostly mild or moderate reactogenicity have been identified. I'd now like to turn to our efficacy evaluation.

So let me now summarize how we went about determining efficacy for the first primary efficacy endpoint. Again, the vaccine doses were administered 21 days apart. And to qualify for the first primary efficacy endpoint evaluation, individuals needed to

have no evidence of prior or current infection before each dose.

And that was determined either by obtaining a swab at the time of each dose, to identify evidence of SARS-CoV-2 by nucleic acid amplification testing, or obtaining a blood specimen for N-antigen antibodies at the time of the first dose to indicate evidence of prior infection that may have preceded vaccination by months.

So this allowed us to be confident that the individuals, for the purpose of this primary endpoint, had no evidence of prior or current infection at the time of each dose. And again, this is important because this is the group that we would all anticipate is most vulnerable to SARS-CoV-2 disease or COVID-19. And then of course as I already mentioned, we have active surveillance for potential COVID-19 symptoms that trigger a telehealth or in person visit and a nasal swab. And we will continue to do this for up to two years after the second dose.

So now let me summarize for you what constitutes a case definition. To qualify as a case for the first primary endpoint case definition, individuals had to be baseline negative by serology and PCR for prior or current infection. And then we characterized the illness as needing to include one or more of these symptoms. And these should be familiar to you because they largely coincide with symptoms that are captured by the CDC case definition, but with a bit more potential specificity. Comparable efficacy observed encompassing all the CDC criteria are shown in the briefing documents.

And then on the right-hand side, once an individual qualifies for those first two categories, they need to have a positive validated PCR; either in our central laboratory or results will be accepted from a local laboratory if it's approved as a type of testing that we agreed is valid. All testing was performed blinded to treatment assignment. And so it's this combination that determines the case definition

for the efficacy results that I'll now be sharing with you.

We performed an interim analysis at 94 cases in individuals without prior infection and observed efficacy of 95.7 percent. We have now also performed the final vaccine efficacy evaluation against COVID-19 occurrence from seven days after dose two in 170 cases without evidence of prior infection. Observed efficacy is high at 95 percent, with high confidence based on the parameters shown in the two right-hand columns.

There's 95 percent probability that efficacy falls in the intervals shown; meaning, that over 97.5 percent likelihood that efficacy is greater than 90 percent. Likewise, the probability that vaccine efficacy is at least greater than 30 percent greatly exceeds FDA COVID-19 vaccine guidance.

This efficacy trial is not powered to evaluate efficacy based on age, stratum, gender, racial or ethnic group. Nonetheless, we think it would be useful for the VRBPAC committee to see vaccine efficacy broken

down by these parameters. As you can see, observed efficacy was high regardless of age and consistent with overall results. Fifteen cases were seen in adults 65 to 74 years of age, and only one was in the vaccine group. Five cases were observed in participants greater than or equal to 75 years of age, and all were in the placebo group.

Likewise, as shown on this slide, efficacy was high in both males and females. And efficacy was high across racial and ethnic groups. Comparable high observed efficacy was observed across white, Black, African American, other racial groups, and likewise also across Hispanic and non-Hispanic ethnicity with lower bounds of the confidence intervals above 80 percent across these ethnic groups. There were also comparable values of observed efficacy seen across geographies.

This efficacy trial was also not powered to evaluate efficacy based on risk groups. Nonetheless, we think it would be useful for the VRBPAC committee to

see vaccine efficacy broken down by these parameters.

The risk groups included individuals with body mass index greater than or equal to 30 kilograms per meter squared, and/or those with Charlson Comorbidity index which included malignancies, chronic pulmonary disease, chronic cardiovascular disease, diabetes, renal disease, and many others. As you can see, observed efficacy was high regardless of whether the participants were at risk or not, consistent with overall results.

Likewise, as shown on this slide, efficacy was high across age groups with and without risk, as well as those with or without obesity. If we break out comorbidity, we see that regardless of category, past history of malignancy, cardiovascular disease, pulmonary disease, diabetes, or additional category of hypertension, point estimates of observed efficacy remain high, and for some, the nominal lower bound of the confidence intervals are well above zero. Hence, we can be confident that the vaccine is likely to work

well in older or debilitated individuals.

Likewise, we have now evaluated efficacy against COVID-19 from seven days after dose two in those with and without prior infection, the second of our two primary endpoints. Efficacy remains high at 94.6 percent with similarly high confidence based on the parameters shown in the right hand columns. It was also important for us to define severe cases both for evaluation of safety and for determinations of efficacy. And for this, we used the definition of severe COVID-19 based on FDA guidance. And that's summarized here for you in bullet form.

ICU admission, clinical signs of severe disease, organ or respiratory failure, and death are key features. Using the FDA definition of severe disease, let's first look at this top table. Although not statistically significant, due to a small number of cases, protection against the few cases of severe disease occurring at least seven days after dose two is consistent with the overall efficacy results, with one

case in the vaccine group and three cases in the placebo group in those without prior infection, shown here.

However, if one examines the All-available population for first severe COVID-19 cases after dose one, the bottom table, only one case is seen in the vaccine group and nine cases are observed in the placebo group for an observed vaccine efficacy of 88.9 percent. The vaccine recipient only met a single FDA criterion for severe disease of O_2 saturation below 93 percent and was not hospitalized.

In contrast, out of the nine placebo recipients with severe disease, six met two or more criteria, six were hospitalized, three were admitted to the ICU, and one was intubated or mechanically ventilated. This is consistent with overall vaccine efficacy seen seven or more days after the second dose, and indicates that the BNT162b2 vaccine is likely to protect well against serious disease.

The FDA's definition does not include

hospitalization as a specific criterion for severe disease. However, the CDC definition of severe disease, shown in the light blue box, includes hospitalization, more severe outcomes of hospitalization, and death. We thought it would be useful to perform a post hoc analysis of severe disease using the CDC definition to further assess the impact of vaccines on this outcome.

Using this parameter, efficacy against severe disease greater than or equal to seven days after dose two was observed, with zero cases in the vaccine group and five cases in the placebo group with confidence interval as shown. Once again, protection was also observed for first severe COVID-19 occurrence after dose one of 92.9 percent with a 1 to 14 case split, and lower bound of the 95 percent confidence interval well above zero. One vaccine recipient was hospitalized 12 days after receiving the first dose of the vaccine, but without additional CDC defined morbidity.

In contrast, of the 14 placebo recipients

hospitalized, three were admitted to the ICU, and one was intubated or mechanically ventilated. This analysis provides further evidence for vaccine protection against hospitalization and attended morbidity.

This curve shows the cumulative incidents of all available COVID-19 cases beginning after dose one. Placebo cases are in red, vaccine cases in blue. Darker dots represent severe cases using the FDA guidance definition, nine in the placebo group and one in the vaccine group, with two instances where cases overlap dramatically at day eight and day 67 in the placebo group.

One can see that by at least 14 days, the curves begin to spread indicating some efficacy after the first dose. Placebo cases continue to increase, out to 105 days at the time of this data cut, while the vaccine case curve remains relatively flat. One can see in this expanded view, from dose one to day 21, that the curves begin to spread by as soon as day 12

and at least by day 14 after the first vaccine dose. This graphic provides -- (Audio cuts out).

DR. ARNOLD MONTO: Hold on a second, Pfizer. We are not hearing you at the moment. So let's just take a moment here to just check on Pfizer's connection. Just out of curiosity, can I get a soundcheck from somebody else, please?

UNIDENTIFIED MALE: Can you hear me?

UNIDENTIFIED MALE 2: Test, test.

DR. ARNOLD MONTO: Okay. Thank you. That's what I wanted. Alright. Hold on a second. We are on a --

UNIDENTIFIED MALE 3: It's them, it's not us.

MR. MICHAEL KAWCZYNSKI: Yep. I figured as much. Pfizer, we are -- we are going to reach out to our sponsor here and tell them that they have to connect their audio. They just -- it looks like they are back up -- they're backup dropped so Pfizer, please go to your backup audio. Here it comes. Are you there, Pfizer?

DR. WILLIAM GRUBER: We're here.

MR. MICHAEL KAWCZYNSKI: Alright. There you go. So, sir just go back about one slide -- just to the beginning of this slide, please. We don't want to lose any of your content. Okay?

DR. WILLIAM GRUBER: Alright. Alright. Thank you.

MR. MICHAEL KAWCZYNSKI: Not a problem.

DR. WILLIAM GRUBER: So apologies --

MR. MICHAEL KAWCZYNSKI: So we'll --

DR. WILLIAM GRUBER: -- to everyone. Are we ready to roll?

MR. MICHAEL KAWCZYNSKI: Alright. So we'll hand it back to -- we're going to -- yep. We're going to hand it back to Pfizer whenever you're ready.

DR. WILLIAM GRUBER: I'm ready. Okay?

MR. MICHAEL KAWCZYNSKI: Alright. Take it away. Yep. Take it away.

DR. WILLIAM GRUBER: Alright. Okay. Great. Thank you. Sorry for the technical difficulties. So

our efficacy conclusions are as follows; both primary efficacy objectives met the success criteria. In individuals without prior SARS-CoV-2 infection observed vaccine efficacy against COVID-19 occurring at least seven days after dose two was 95 percent with high probability, 97.5 percent that the true vaccine efficacy is at least 90 percent. And again, this meets the pre-specified FDA criteria for Emergency Use Authorization.

Observed vaccine efficacy was greater than 93 percent for the first primary endpoint across age, race, ethnicity, and at-risk subgroups. Per the FDA definition, nine severe COVID-19 cases were observed in the placebo group and one in the vaccine group as of the interim analysis cutoff dates, and 14 hospitalizations and associated morbidities were seen in placebo recipients versus one vaccine recipient hospitalization in a post hoc analysis, providing further evidence to support efficacy against severe disease consistent with that seen against all COVID-19.

From the cumulative incidents curve, there is early onset of protection with divergence of the placebo group from the BNT162b2 group as soon as 12 days, and by at least 14 days with steady accumulation of cases in the placebo group while the vaccine group remains virtually flat. Overall, the efficacy results show that the vaccine at 30 micrograms provides protection against COVID-19 in participants who had, or did not have, prior SARS-CoV-2 infection and COVID-19.

Our Emergency Use Authorization application is based on our satisfactory safety profile and efficacy against COVID-19. The Emergency Use Authorization will be seeking an indication for individuals who are 16 years of age and older. This safety data includes reactogenicity in over 8,000 individuals.

Adverse events and serious adverse events in over 37,000 individuals with a median of two months of follow up post dose two, and adverse events and serious adverse events at over 43,000 individuals 16 years of age and older with varying degrees of follow up. The

BLA, which we plan to submit in 2021 will encompass reactogenicity in over 8,000 individuals and AEs and SAEs in at least 44,000 total participants. Of these, safety data will be provided from at least 6,000 participants with six months or more of safety follow up post dose two.

Additional data will include safety in a 12 to 15 year old population which is currently undergoing study as part of our current Phase 2/3 trial. The efficacy that we have presented to you today is based on more than 164 SARS-CoV-2 cases and immune response in adults 18 years of age and older. This also serves as the foundation of data for the BLA which we plan to file by April of 2021. Additional planned analyses include efficacy against asymptomatic infection, evaluation for persistence of protection, and a 12 to 15 year old immuno-bridging study.

As you will note in the Pfizer briefing document, we plan to administer vaccines to placebo recipients. We have an ethical obligation to inform

study participants of COVID-19 vaccine availability under Emergency Use Authorization. We are currently in discussions with the FDA about the best way to vaccinate placebo recipients to further inform safety and efficacy of the vaccine while meeting our ethical obligations to participants. Eligible participants in the placebo group will have the option to receive the vaccine.

Since it will take to provide vaccines to over 22,000 placebo recipients, we plan to first offer vaccines to those individuals satisfying FDA Emergency Use Authorization and current CDC recommendations. Vaccination of other participants will expand over time. Participants will be given the option to remain blinded if they chose to do so through study completion. The study will continue for the planned 24 months regardless. Pfizer plans to meet FDA EUA guidance for risk and benefit during use of the vaccine under the Emergency Use Authorization.

First, let's talk about pharmacovigilance.

Since this vaccine is likely to be administered in a short time, we've expanded our capacity to process AE reports with an online adverse event reporting portal. Our signal detection activities will occur on a more frequent site. We have plans for future clinical studies to expand to more vulnerable populations.

Second, proactive risk minimization. Clear, comprehensive labeling and education materials for vaccine providers will emphasize key messages about appropriate handling, storage, and preparation of the vaccine. And for vaccinees, emphasize the importance of following up for their second dose to maximize their protection. Product in cold-chain will be monitored in real time.

Third, pharmacoepidemiology studies. Several safety studies are planned to continue safety data collection. These will access healthcare information from millions of lives to monitor safety events including adverse events of special interest. We know our vaccine works in the clinical study setting and

plan to investigate its effectiveness in real world use.

And finally, collaborating with vaccine safety stakeholders. At a previous VRBPAC and this morning, we've heard about the FDA and CDC's planned programs for pharmacovigilance, including VAERS, CISA Network, V-SAFE, and VSD, and we've shown you some of our plans which are intended to be complimentary to CDC and FDA planned pharmacovigilance activities. After approval, Pfizer will conduct test-negative design studies to demonstrate real world effectiveness against severe disease with important endpoints like hospitalizations and emergency department visits in specific populations and to understand vaccine efficacy when vaccine is used in real world conditions and in broader populations.

These studies will complement the CDC planned effectiveness studies. We also intend to conduct a number of studies recognizing that there are other populations that stand to benefit and there are other things that we need to learn about the vaccine. These

include boost-ability, studies in pediatrics and pregnancy, and use in immuno-compromised populations. We also plan to explore a refrigerator stable next generation formulation that can combinate use with influenza vaccine.

We look forward to expanding the safety, immunogenicity, and efficacy profile demonstrated today. So now that ends my summary of the clinical development program and I'm pleased to turn our presentation back over to Dr. Kathrin Jansen.

DR. KATHRIN JANSEN: -- Dr. Gruber. We believe that our data have satisfied the EUA requirements for a COVID-19 vaccine as you see here on the green checkmarks. We are seeking Emergency Use Authorization for our vaccine for prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years and older with or without evidence of prior infection with SARS-CoV-2.

We have demonstrated the positive benefit-risk profile for our BNT162b2 vaccine given the high overall

vaccine efficacy of 95 percent with high efficacy observed in both younger and older adults, as well as diverse demographics with and without underlying comorbidities. And we observed efficacy against severe COVID-19. In addition, we have demonstrated a favorable safety and tolerability profile in more than 40,000 individuals.

So why are we applying an Emergency Use Authorization for BNT162b2 now? With the high efficacy and good safety profile shown for our vaccine and the pandemic essentially out of control, vaccine introduction is an urgent need. Dramatic increases in cases have occurred all over the country and it is estimated that about 55,000 deaths will likely occur every month over the next few months. Modeling from the CDC shows that a vaccine with high efficacy can save many lives.

However, a pandemic vaccine must be introduced before the peak of cases to have maximal impact which is best achieved under EUA. We at Pfizer

and BioNTech wish to thank all of our sites, investigators, and their dedicated staff. And we want to thank our clinical trial participants without whom we would not be here today. We are also grateful for the guidance provided by the CDC, the FDA, and other regulatory bodies, and members of Operation Warp Speed.

Finally, we want to thank our colleagues at BioNTech, Pfizer, and other companies for their tireless work and dedication to develop our COVID-19 vaccine candidate. Thank you for your attention and we would be happy to take any questions.

DR. ARNOLD MONTO: Thank you very much to both of you. I wanted first to ask Dr. Gruber about how he is going to be measuring asymptomatic infections. In addition, I wanted to let everybody know that Bill Gruber is not related to Marion Gruber. So, Bill.

DR. MARION GRUBER: That's correct. Not to my knowledge.

DR. KATHRIN JANSEN: Alright. If I understood you or heard you correctly because there was a little

bit of a delay, you were asking about our plans how to monitor asymptomatic infections.

DR. ARNOLD MONTO: Correct.

DR. KATHRIN JANSEN: So indeed, our protocol, our trial was actually designed not just to look for symptomatic COVID-19, but also to monitor and explore whether our vaccine is efficacious against asymptomatic infection. And we are monitoring individuals and screening them with a serological test that measures exposure to SARS-CoV-2 infection N-protein test.

DR. ARNOLD MONTO: Right. The N-protein. Yes.

DR. KATHRIN JANSEN: And we hope -- yes -- and we hope that we will have those analysis completed very soon in the new year.

DR. ARNOLD MONTO: And you were also looking then at correlates of protections?

DR. KATHRIN JANSEN: That is correct. Our -- in our large study with collecting serological samples throughout the study up to study conclusion, which is

24 months duration, we have the opportunity to look for correlates of protection provided that we see enough breakthrough cases over time --

DR. ARNOLD MONTO: (Audio distortion).

DR. KATHRIN JANSEN: That's right. So of course with a vaccine that is highly efficacious, and if it continues to be highly efficacious over time, it may be a little bit more difficult to define a correlate of protection but nevertheless we are trying. We are trying to do that.

DR. ARNOLD MONTO: Okay. We have many, many questions and we're going to have to limit them and hope you -- and expect you to stay on for our open discussion in about an hour or so because I think we can get to some of the other issues at that point. So Dr. Levy.

DR. OFER LEVY: Hi. Thank you. I'm Dr. Ofer Levy with the Precision Vaccines Program at Boston Children's Hospital. I'd like to thank Pfizer for its impressive effort and excellent presentation. I have

the following questions. For Dr. Jansen, one regarding mechanism of action. RNAs, in principle, can be recognized via the innate immune system. Specifically, potential RNA boost activation of Toll-like receptor 7 and 8 could induce interferons, which may explain the transient lymphocytopenia that was observed in the study and may provide an adjuvant effect contributing to robust immune responses and the protection observed.

Recognizing that the vaccines contains modified RNA that may have blunted innate immune activating potential, what is known regarding the ability of the lead mRNA to activate Toll-like receptors such as TLR-7 and 8? Has the mRNA vaccine induced BLR activation been assessed in vitro in cell culture?

And my question for Dr. Bill Gruber regarding the safety, the briefing document alludes to numerical imbalances of AEs potentially representing allergic reaction. What is Pfizer's knowledge regarding any potential vaccine AE relating to allergic reactions

from either animal models or human data? And finally, regarding immunogenicity, Dr. Gruber described the adaptive response. What about the innate? Were plasma, cytokines, chemokines measured and did these correlate with any of the study endpoints? Thank you.

DR. KATHRIN JANSEN: Yeah. So I would like to actually have Dr. Sahin describe in detail what we know about the mechanisms of action. Let me just start out while Dr. Sahin is getting ready to say that one of the reasons that we chose the modified RNA platform for the -- for our vaccine is the reason that indeed it tempers if you want -- tunes down if you want, the innate immune system. Because as I mentioned earlier, we were looking for a candidate that would allow us to have a very -- or would give us a vaccine with a very favorable safety profile. If I could ask Dr. Sahin please to come -- to comment on the more detailed questions about signaling pathways for the mRNA vaccine candidate.

DR. UGUR SAHIN: Yeah. Can you hear me? It's

good volume?

DR. KATHRIN JANSEN: Yes.

DR. UGUR SAHIN: Yeah.

DR. KATHRIN JANSEN: Yes.

DR. UGUR SAHIN: Thanks, Kathrin. This is indeed an excellent question broached. The nucleotide modified mRNA does not directly activate TR-7 and TR-8 in the human setting. And adjuvant activity is driven by a combination of the recognition of messenger RNA component (inaudible) lipid nanoparticle formulation, which disrupts the integrity of the plasma membrane, which integrates innate immune stimulation signals that will start an activation of the (inaudible) pathway. And this starts in cytokine secretion with starting in the lymphocyte recirculation from the blood into the peripheral tissue.

DR. KATHRIN JANSEN: Thank you. Bill, you want to touch on the other part of the question?

DR. WILLIAM GRUBER: Sure, Kathrin. And we can obviously, if there are additional questions,

follow up in terms of pharmacovigilance. But I think the first question was about adverse events within the study. Amongst the 44,000 subjects, we saw no serious allergic reactions to the vaccine.

There were no substantive differences in standard measure queries in numbers between the BNT construct and the placebo groups analyzed on the 38,000 subject database. So within the clinical trial, we've actually not seen evidence to suggest a signal related to allergic reaction to the vaccine. Obviously, we're conscious of the report that's occurred with use in the U.K. and perhaps Patrick Caubel can speak to that.

As far as the -- and maybe while he's preparing let me just deal with the second part of your question, which was the nature of cytokine measurement and the like. The measurements that were obtained were the ones that I shared with you. And I think, actually, as of today it's my understanding that it's now being published from the Phase 1 trial -- from the German trial, some of which I shared with you in

talking about the CD4 responses. But we have not as part of either our Phase 1 trial in the United States or the Phase 2/3 expansion looked specifically at cytokines as part of that trial.

DR. OFER LEVY: Thank you.

DR. KATHRIN JANSEN: Thank you.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Moore.

DR. PATRICK MOORE: -- exciting data. Thank you very much. Perhaps the most interesting data I've heard in this epidemic. There -- I have two questions for you. One is related to Ofer's question, which is modified RNAs in this vaccine.

Do we know anything about whether the modified RNAs undergo salvage, could be reincorporated into, for instance, DNA, or if cellular reverse transcriptases could possibly amplify them or turn them into DNA? That's one question. The second one is, among the eight people that were vaccine failures, do you have -- did -- were you able to sequence the virus that came

from those people, and was there evidence of antibody escape from your antigen?

DR. KATHRIN JANSEN: Yeah. So I will start to -- with answering the last -- your last question and then I'd like to get Dr. Phil Dormitzer to be ready to address your first question. So as of the eight individuals that had a vaccine failure in our study, we have not yet analyzed, for example immune responses or anything else for those individuals but we plan to do this. But we don't have the data today. And if I could ask Dr. Dormitzer to answer the question that you had about the RNA.

DR. PHILLIP DORMITZER: Yes. I guess there were two questions. One is of the modified nucleotides recycled, the RNAs? The second about the possibility of reverse transcriptase change -- transforming the RNA to DNA. We do not have data on recycling of the modified nucleotide.

Although it's theoretically possible for a reverse transcriptase to act on RNA, we think that the

probability is actually quite low that this would occur. mRNAs have no signals that would make them preferential substrates for a reverse transcriptase. They are present transiently in literally low amounts.

And we actually have very recent data indicating that actually, it's a very modest amount of RNA that gets into the cell. We actually don't see it hitting the nucleus where this would occur so there don't seem to be any greater likelihood that a vaccine RNA would end up reverse transcribed than a cellular RNA.

DR. KATHRIN JANSEN: Thank you.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Offit.

DR. PAUL OFFIT: Yes. Thank you. So this question is probably for Bill. First of all, thank you for an excellent presentation. The -- one thing that's been raised is that there roughly were 162 participants who got sick that were in the placebo group, which would mean a disease rate of about 0.74 percent. It

seems like that might be low.

But -- so would be interesting to know whether that was lower than the disease rate in the area where the participants were being recruited. Because the concern that if that is true, if it is lower than typical, that we may have an example of volunteer bias where people who volunteer for this trial are more likely to physically distance, more likely to wear a mask, and therefore, more likely to be exposed to a lower inoculum.

So could you comment on that? Was that 0.74 percent disease rate lower than you were seeing in that area? Was that typical for the areas where you were recruiting?

DR. KATHRIN JANSEN: Bill?

DR. WILLIAM GRUBER: Yeah. I think, of course, it's a good question, Dr. Offit. I -- the rate of disease that we were seeing I think was relatively typical of not only the area but thinking ahead to the nature of this population, on the one hand, this is a

population that we recruited because they were at increased risk. But they were also voting with their feet to be part of a vaccine trial and hence we assume that of course, they were, and we certainly encouraged them to take the appropriate sorts of social distancing measures and masking. So I expect it was probably some combination of the two.

The other thing to keep in mind is that this trial, although it's been very, you know, short duration in terms of being able to get our efficacy endpoint, did span a period of time particularly in the United States where rates dropped. And then of course we now know the horrific situation we're in now with over 3,000 deaths a day. But it's my sense that part of this is the nature of the span of the trial both during a time when the rates were high and low, as well as the precautions that individuals in the trial, even though they were high risk, took to further reduce that risk.

DR. PAUL OFFIT: Thank you.

DR. KATHRIN JANSEN: Thank you.

DR. ARNOLD MONTO: Okay. Dr. Pergam.

DR. STEVEN PERGAM: Thanks. First of all, I just want to thank Pfizer again for first of all presenting this data. And I want to -- I really thank them for providing this data to the public as well because I think the way that they present this data to the community was really important for many different reasons. I've been curious about enrollment related to risk categories.

It, you know, the large proportion of people in this trial are white and there's about, I think I characterized 46 percent had a comorbidity and a certain number were of older age, et cetera. My curiosity is about timing of enrollment and on those high-risk groups. Were they more likely to be enrolled in latter portions of the trial and therefore had less time accumulated and at risk? Do you have data about how many people have been followed for two moths versus four months, et cetera, in the time and risk strata?

I'd be curious if that makes a difference in terms of the outcomes we're seeing.

DR. KATHRIN JANSEN: Yeah. So we have the -- all the individuals 18 and older were part of our study right from the get-go as well as all of the risk groups. The only individual participants that were invited later as part of the study were the younger age group, the 12 to 15-year-olds, the 16 to 18-year-olds, and individuals that had stable underlying infectious disease conditions such as stable HIV, Hepatitis-B or Hepatitis-C.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Banacloche.

DR. JUAN GEA-BANACLOCHE: Thank you. My question is, how sure are you that you need the second dose, the booster dose? And the reason I'm asking is that clearly in the Neurological for Medicine paper, you can see that the responses are much better after the second dose, but in the graph where you show the two curves separating, they separate at 14 days. And

they -- the curve remains flat so you cannot see any effect of the second dose on the curve and I wonder if there's a possibility that one dose is enough. If it is not, how do you know it's not?

DR. KATHRIN JANSEN: So we are obviously interested to evaluate in our vaccine study the persistence of protection over time and so the data that we have so far, and if could have up the Kaplan-Meier curve, not the insert but the whole curve, please? If someone could have that slide up. What you see on that slide that so far, we have -- slide three up, please. So you see that so far, we were able to observe high degree of efficacy for up to 105 days or so. And I think it's really important that we do understand what the persistence is of our protection.

So we cannot conclude to say that after single dose we would see a similar persistence of infection. So, therefore -- and we also have seen that protection was most mature and was highest after two doses were given. So therefore, while we won't have the data to

look at one dose versus two doses, but since we started this study with two doses we, of course, cannot predict how a single dose would affect vaccine persistence or protection of persistence which is very -- which is of course very important in this setting.

DR. ARNOLD MONTO: Okay. I'm going to -- the last question that we're going to have in this session, and we'll try to pick this up when we have more time in the discussion later on is Dr. Hildreth. Dr. Hildreth, the floor is yours.

MR. MICHAEL KAWCZYNSKI: Dr. Hildreth, make sure you don't have your own phone muted. You are unmuted in the system.

DR. JAMES HILDRETH: I'm sorry. I did not have a question. My question was asked and answered already.

DR. ARNOLD MONTO: Okay. Well, in that case, we'll move on, at least temporarily. Please stay available so we can return to some of these questions in the first part of our discussion. Now I'd like to

call on Dr. Wollersheim from FDA who is going to give us FDA's presentation of the data and also describe the questions we are going to address in the discussion. Dr. Wollersheim.

FDA PRESENTATION AND VOTING QUESTIONS

DR. SUSAN WOLLERSHEIM: Thank you so much, Dr. Monto, and good afternoon everyone. I'll go ahead and present our FDA review of the clinical data submitted with the Pfizer-BioNTech COVID-19 vaccine Emergency Use Authorization request. Alright. So brief outline here just to walk you through what we're going to present today.

I'll start with a brief introduction of the product and an overview of the clinical development program followed by our efficacy and safety data analyses. Then review the pharmacovigilance plans and plans for future and ongoing studies. And finally, ending with our benefit-risk assessment to help prepare

the advisory committee to discuss and vote on the topics presented earlier today by Dr. Fink.

So first we will begin with a brief introduction and Pfizer just walked us through this. The vaccine is based on the SARS-CoV-2 spike glycoprotein S antigen encoded by RNA and it is a formulated in lipid nanoparticles. It's administered by two intramuscular injections 21 days apart with proposed indication and usage under the EUA. It's for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

And moving on to a brief overview of their clinical development programs to date. There are two ongoing studies of the vaccine candidate. Study BNT16201 is an ongoing Phase 1 dose-finding safety and immunogenicity study in adults 18 to 50 years of age. And study C4591001 is an ongoing Phase 1/2/3 randomized placebo controlled, observer blinded study in individuals 12 years of age and older.

I'll note now, as Pfizer also pointed out, that their Phase 1 studies did begin at approximately the same time earlier this year, BNT16201 in Germany and C4591001 in the U.S. The overlap of vaccine candidates and dose levels in the two studies allowed for phasing immunogenicity from each study to provide data and support in real time to change vaccine candidates and dose levels to be evaluated in a larger study that began in the U.S.

So looking at study BNT16201, this study evaluated 60 participants who received the vaccine candidate BNT162b2 at the various dose levels listed in the table. There are 12 participants per dosage cohort and no placebo group. The safety results showed a similar safety profile for the vaccine candidate between both Phase 1 studies. There are no serious adverse events reported in the safety database for BNT162b2.

And moving on to the immunogenicity results. These results were obtained seven days after dose two

and show that two doses of the vaccine candidate induce SARS-CoV-2 neutralization antibodies, with geometric mean titers comparable to or higher than GMTs from a human convalescent serum panel from recovered COVID-19 patients. The GMTs are highest with the 30 microgram dose.

Two doses of BNT162 also induced S-1 binding immunoglobulin G antibodies and a T-Helper 1 skewed secretion of interferon gamma and or IL-2. The immunogenicity data demonstrated a prospect of benefit to support enrollment of larger numbers of subjects. And thus the data from study BNT16201 helped support the final vaccine candidate, selected dose, and vaccination schedule that was determined in tandem with the Phase 1 data from study C4591001.

We'll move on to that study design next. And initially, the study was designed to include approximately 30,000 adults 18 to 85 years of age. And this study population was expanded after the study was already underway to later include participants down to

12 years of age and those with stable, chronic medical conditions, and infections such as HIV, Hepatitis B or C.

All participants were planning to receive two doses of the vaccine or placebo 21 days apart. The Phase 1 portion of this study was designed for dose-finding and vaccine candidate selection based on evaluations of safety and immunogenicity. 90 participants are randomized 4 to 1 to receive vaccine of placebo in cohorts of 15 per dose-level separated into two age groups of participants 18 to 55 years of age and 65 to 85 years of age. The dosing began at the lower dose levels and participants in the younger age group, and the doses escalated only after safety review. In the older age group was vaccinated with the same vaccine dose and candidate following a satisfactory safety review of the same dose in the younger age group.

The numbers of participants who received the various dose levels of the two vaccine candidates

evaluated are displayed there. These Phase 1 results in combination with the study BNT16201 determine the final vaccine candidate to move forward into Phase 2 and 3. Alright. Let me go one back here.

And the study design for Phase 2 and 3 included a randomization of 1 to 1 for participants to receive either the vaccine candidate or placebo and to evaluate the safety and efficacy of a vaccine candidate. The first 360 participants enrolled were specified as an expanded cohort to further evaluate safety and immunogenicity. And any COVID-19 cases from these participants also contributed to the overall Phase 3 efficacy population.

Enrollment was stratified by age as displayed with a goal of 40 percent in the oldest age group representing a population at risk for COVID-19. The total number of participants 60 years of age or older that were randomized in the Phase 2 and 3 as of November 14th was 43,551. And here is a graphic to show the overall study designed as planned with a point

in time for the data cut off identified in yellow for which we have the data to present to you today.

Participants either received vaccine or placebo 21 days apart and surveillance for potential COVID-19 symptoms began after the first dose. The presence of any of these symptoms would trigger an illness visit for collection of the details about the symptoms and collection of a nasal swab for PCR testing. Additionally, participants had blood drawn prior to dose one as well as nasal swabs prior to each dose for SARS-CoV-2 PCR testing to evaluate for the evidence of baseline infection.

Participants were vaccinated and followed immediately after each vaccination for 30 minutes for any acute reactions, and then also followed for unsolicited adverse events for one month after their last dose, and for serious adverse events for six months after their last dose. A subset of participants were designated as the reactogenicity subset and reported daily solicited adverse reactions for seven

days following each dose. All participants are planned to have two years of follow up for possibly related serious adverse events or deaths as well.

Moving on to the case definitions here. On the right-hand side of the slide is the case definitions of the primary endpoints which included at least one of the listed symptoms and a positive SARS-CoV-2 PCR test obtained within four days of the symptomatic period. And on the right side of the screen is the case definition for one of the secondary efficacy endpoints which is severe COVID-19 disease.

This case definition was met for confirmed COVID-19 cases as shown on the right who also had any one of the listed more severe criteria based on vital signs, the need for medical intervention for respiratory failure, shock, intensive care unit admissions, or death. And moving on to the primary efficacy endpoints. The primary endpoint definition was using the case definition from the previous slide, confirmed COVID-19 cases that occurred at least seven

days after dose two were counted towards the primary endpoint. From the first primary efficacy endpoint was described in terms of COVID-19 incidence per 1,000 years of follow up and those without serological or virological evidence of past SARS-CoV-2 infection before or during the vaccine regimen.

Evidence of past SARS-CoV-2 infection was based on the result from the baseline blood draw to evaluate for the presence of SARS-CoV-2 antibodies prior to dose two, and the results from each PCR test done prior to each dose. All of which needed to be negative results for participants to be included in the first primary endpoint. The second primary endpoint -- efficacy endpoint was described in the same terms but in participants with and without evidence of prior infection. The secondary efficacy endpoints are listed here based on different case definitions and time cut off for counting those cases.

The first endpoint listed is for confirmed COVID-19 cases that occurred at least 14 days after

dose two and those without, and with and without evidence of past infections. The second endpoint is confirmed severe COVID-19 cases that occurred at least seven or 14 days after dose two, and those with and without evidence of past infections. The final endpoint is confirmed COVID-19 based on the CDC case definitions occurring at the same two timepoints and two participant populations.

And now the next slide will review the statistical considerations for the primary endpoints. The vaccine efficacy was evaluated in participants without evidence of prior infection before two -- seven days following the second dose in the evaluable efficacy populations, which I will define for you on the next slide. And vaccine efficacy was defined in terms of illness rate ratio, or IRR, where the IRR is calculated as a ratio of the first confirmed COVID-19 illness rate in the vaccine group to be -- to the corresponding illness rate in the placebo group.

For the interim and final efficacy analyses

the success criterion was met if the lower bound of the vaccine efficacy was greater than 30 percent based on the numbers listed for the interim and final analyses above. Interim analyses were planned after the accrual of at least 32, 62, 92, and 120 cases, but in reality, the first interim analysis was conducted upon accrual of 94 cases on November 4th and it met the success criterion outlined here. The final analysis was planned after accrual of at least 164 cases. And in reality, it was conducted upon accrual of 107 cases on November 14th.

And now to define for you the analysis populations that will show from our data analyses today. The populations and the numbers of participants who were included in these populations are presented here. The All-available efficacy populations included all Phase 2 and 3 randomized participants who received at least one or two study vaccinations and the invaluable -- hello? Okay.

The evaluable efficacy populations was a

subset of this group. The participants who received all vaccines within the predefined time window without important protocol deviations and with follow up through November 14th. The evaluable efficacy population was used for the primary efficacy population.

In terms of the safety populations analyzed, the All-enrolled populations included all enrolled participants regardless of the duration of follow up who received at least one study vaccination. And the study population was -- the safety population was a subset of this group for participants who received at least one study vaccination and were enrolled through October 9th with follow up through November 14th.

So to review the duration of follow up for the Phase 2 and 3 participants in terms of our guidance for the EUA for the COVID-19. For this study, I think it's important that the sponsor submitted protocol revisions while the study was underway to increase the sample size and to expand the study population. So there was

a late enrollment for participants in the adolescent age group, and those over 85 years of age, and those with stable, chronic infections such as HIV, Hepatitis B or C. So these specific study populations do have less follow up than the general study population.

But for the evaluable efficacy population, the participants included in the interim analysis conducted on November 4th at a follow up duration of less than two months. And the interim analysis was successful with a vaccine efficacy of 95.5 percent after the accrual of 94 cases. The participants included in the final analysis conducted on November 14th also had a follow up duration of just less than two months.

However, this time point included all of the participants included in the interim analysis, and the duration of follow up for the participants included an interim analysis at the time of the final analysis is two months. We focused our review, however, on the data from the final efficacy data cutoff, which includes those from the interim analysis, because the

results of the final analysis were consistent with those from the interim analysis and they provided more robust data from a greater number of participants.

The Phase 2/3 safety populations includes only Phase 2/3 participants enrolled by October 9th with a follow up through November 14th, and the median follow up duration is two months. The All-enrolled population includes all enrolled participants regardless of the duration of follow up. And the median duration of follow up for this group is less than two months. But additional safety analyses from this larger database of All-enrolled participants was also reviewed to evaluate for differences compared with the smaller Phase 2/3 safety population.

And this is just a duplicate slide. So moving on to one additional consideration that we wanted to point out was implemented for vaccine-induced enhanced respiratory disease. There's oversight from the data monitoring committee from day one. And an unblinded team supporting the DMC reviewed cases of severe COVID-

19 at least weekly to evaluate the case splits of the number of severe cases in each treatment group in terms of the study design alert criteria and stopping rules that are outlined in this slide.

Neither the alert trigger nor the study stopping criteria were met, which suggests that vaccine administration was associated with more severe COVID-19 disease to date. And now I will go ahead and move on to our efficacy data analyses. And the first slide here is showing the demographics of our efficacy population by demographic subgroup such as sex, age, race, ethnicity, and the presence of comorbidity.

For age, you can see that the elderly population is represented with approximately 20 percent of the population being 65 years of age and older. For race, approximately 10 percent of participants identified themselves as Black or African American. And there are smaller numbers of participants of American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and multiracial backgrounds.

In terms of ethnicity, approximately 25 percent of the population identified themselves as Hispanic or Latino. And approximately 45 percent of the population had medical comorbidities, specifically, 35 percent of the population was obese. You can also see here that there are 153 total adolescents, 16 to 17 years of age that were included in the efficacy population. The demographics are similar for the safety population.

So moving on to the dispositions of the efficacy population. To identify the reasons for exclusion from the evaluable efficacy population for analysis of our primary endpoint. Starting at the top of the slide, from the total number of randomized participants and moving down the table you will see how many subjects received each dose and were included because they did not have evidence of prior infections, in addition to how many subjects were excluded with the reason for exclusion listed toward the bottom of the slide.

Most of the exclusions were because participants did not receive both vaccinations within the predefined windows, and the number of participants affected was balanced between treatment groups. There were more protocol deviations in the vaccine group than the placebo group, and most of them were medication errors such as product storage errors, incorrect dosage administration, or the wrong product being administered.

The next slide here shows the results of the primary efficacy analysis with a total 170 cases, 8 in the vaccine group and 162 in the placebo group giving a vaccine efficacy of 95 percent for the prevention of COVID-19 from seven days after dose two. And the criterion for success was met. The prespecified age stratifications are also shown here with similar results for vaccine efficacy.

On this slide the first row shows the overall second primary efficacy endpoint, which is COVID-19 cases at least seven days after dose two in subjects

with and without prior infection as most people who will receive the vaccine most likely will not know their baseline infection status. The vaccine efficacy was similar to the primary endpoints and had nine cases in the vaccine group and 169 in the placebo group, giving a vaccine efficacy of 94.6 percent.

Subgroup analyses of this second primary endpoint are also shown here by age, obesity as a comorbidity, and by sex. The vaccine efficacy was consistently high across different subgroup analyses with limitations on the adolescent age group because of small numbers of cases and participants as compared to the adult population. The vaccine point estimates were uniformly high across the subgroups examined, with the exception of participants identifying as multi-racial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 occurred to interpret efficacy data for these subgroups.

So continuation of the subgroup analyses for

the second primary endpoints are shown here. I think I just described that with the prior slide. So the vaccine efficacy point estimates were uniformly high so you can see the numbers here on this slide.

And moving on to one additional subgroup analysis of the vaccine efficacy by comorbidity to show that the vaccine efficacy point estimates, again, were uniformly high across subgroups, again, that increase the risk of COVID-19 such as chronic pulmonary disease, diabetes, obesity, and hypertension. The next slide here is to show that the secondary efficacy analyses have similar case splits. And the vaccine efficacy results are consistent with the primary efficacy endpoint for these secondary efficacy endpoints, as well, based on the case definitions with cases being counted at 14 days following dose two as well as using the CDC case definitions.

The other secondary efficacy to discuss is severe COVID-19 and this table breaks down the numbers of severe cases that occurred in the All-available

efficacy populations at each range of timepoints shown following dose one. In the All-available efficacy population, 10 participants have severe COVID-19 disease after dose one; one subject who received the vaccine, and two subjects who received placebo. The vaccine efficacy was 88.9 percent but within a wide 95 percent confidence interval that goes down to 20 percent.

Based on review of the case managers overall, and the All-available efficacy populations, two placebo recipients met severe criteria based on vital signs and no other criteria. Six placebo recipients who had severe COVID-19 disease were hospitalized, three of which were admitted to intensive care unit and seven placebo recipients had at least one risk factor for severe disease. In the bottom row of this table, you see the case splits for the primary endpoint evaluations at least seven days after dose two, in which four placebo recipients and one vaccine recipient had severe COVID-19 disease.

The vaccine recipient who had severe COVID-19 disease met the severe case definition because of oxygen saturations at the time of the COVID-19 illness visit being less than 93 percent on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease.

The four placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had oxygen saturation of 92 percent on room air and one had a heart rate of 125 without other severe criteria; one subject was hospitalized for non-invasive positive pressure ventilation with bilateral pneumonia; one subject had an oxygen saturation of 92 percent and ICU admission for heart block. Two of these placebo recipients with severe disease also have obesity as a risk factor while the other two participants did not have any risk factors for severe disease.

The total number of severe cases is small,

which does limit the overall conclusions that can be drawn. However, the case split does suggest protection from severe COVID-19 disease. We'll move on to one post hoc analysis that we ran on the timing of COVID-19 cases following dose one and the All-available efficacy population.

The timing of cases is presented similarly to the prior slide for severe cases. Vaccine efficacy and participants in the All-available efficacy population were similar to results in the evaluable efficacy population. And the vaccine efficacy for prevention COVID-19 disease after dose one is 82 percent.

Based on the number of cases accumulated after dose one and before dose two you can see that there does seem to be some protection against COVID-19 disease following one dose. However, these data do not provide information about longer term protection beyond 21 days after a single dose because the vast majority of subjects received dose two. And our next slide here shows one additional post hoc analysis of the vaccine

efficacy based on baseline SARS-CoV-2 status in the dose one All-available efficacy population.

Only three percent of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study; 10 in the vaccine group and nine in the placebo group. Only one of the 10 cases in the vaccine group occurred seven days or more after completion of the two-dose vaccine regimen. Some participants with prior evidence of infection also had confirmed COVID-19 during the study conduct.

These data do suggest that previously infected individuals can be at risk of COVID-19 reinfection. The small numbers of participants with baseline positive status limits the interpretation of the efficacy at this timepoint. Moving on, we will now focus our attention on the safety data, and here's a quick reminder from the graphic about the general study design.

And first, we'll review, the reactogenicity results collected daily for the first seven days following each dose in the reactogenicity subset. Dose one reactogenicity is shown here on this first slide and it's separated by the pre-defined age stratification. For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose two, the younger age group reported any pain more frequently than the older group, and pain was characterized as moderate with a similar pattern observed after dose one.

Injection site redness and swelling after each dose was generally similar for both age groups. For each age group in the reactogenicity subset, the younger subjects and overall the median onset of local reactions in the vaccine group was from the day of vaccination to two days after the dose and lasted for a median duration between one and doses -- one and two days. Local reactogenicity following dose two is shown here with consistent reports of pain, redness, and

swelling. An analysis by various demographic subgroups showed consistent results.

The next slide here shows -- my slides are a little behind. I'm sorry. So here are solicited adverse events within seven days following dose one. I'm caught up. I apologize for that. These are -- let me catch up here.

These are reports of joint pain, diarrhea, and vomiting which were reported pretty equally between the age groups and the…. Following dose two the systemic reactogenicity is shown here. The frequency and severity of systemic AEs was higher after dose one than in dose two -- was higher after dose two than dose one except for vomiting and diarrhea, which is generally similar regardless of dose. And again, analyses by various demographic subgroups showed consistent results.

This slide is a continuation of the dose two solicited systemic adverse reactions within seven days showing the numbers for joint pain, diarrhea, and

vomiting. Here are the numbers for our adolescents 16 and 17 years of age. It's important to note that the majority of adolescents 16 and 17 years of age enrolled by October 9th, local reactions, and systemic AE data were collected as unsolicited AEs with the preferred terms showed here, rather than from prespecified prompts for reactions which were solicited daily for seven days for each vaccination as was done for the adult population just shown.

So the same details are not available for reactogenicity in 16 and 17-year-olds as compared to the adults in the study at this timepoint. So based on the unsolicited AEs shown here, in general, the 16 and 17-year-olds had similar symptoms reported but to a lesser degree than the adult population. Moving on to the unsolicited adverse events. Subjects were monitored for 30 minutes immediately following each vaccination and no subjects had an acute allergic reaction.

For the unsolicited non-serious adverse events

that were reported more frequently in the vaccine group than the placebo group, they're consistent with solicited reactions recorded from the reactogenicity subset; 18 percent in the vaccine group versus three percent in the placebo group, which would be expected. Additionally, lymphadenopathy occurred more in the vaccine group than the placebo group with a plausible relationship to vaccination.

And finally, Bell's Palsy occurred in four vaccine recipients and no placebo recipients, two within one month of vaccination and two after one month. More details here include that three cases occurred at 3, 9, and 37 days after vaccination and participants with no prior history of Bell's Palsy. The case with the onset at three days post-vaccination was reported as resolved without (inaudible) within three days of onset.

The other case -- the other three cases were reported and continuing or resolving as of the November 14th data cutoff with ongoing duration of 15 -- 10, 15,

and 21 days, respectively. The fourth case had an onset at 48 days after vaccination in a participant with prior history of Bell's Palsy. And it was reported as ongoing with a duration of 21 days at the time of the data cutoff.

In addition, we independently conducted standard measure queries, SMQs, using FDA developed software to evaluate for a constellation of unsolicited adverse events -- event preferred terms that could represent various diseases and conditions including but not limited to; allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs conducted on the Phase 2/3 All-enrolled safety population revealed a slight numerical imbalance of adverse events potentially representing allergic reaction, with more participants reporting hypersensitivity adverse events in the vaccine group with 137 or 0.63 percent compared with the placebo group with 111 or 0.51 percent. There are no imbalances between treatment groups that were evident for any other SMQs evaluated.

Moving on to serious adverse events. There were six deaths reported in the study, two in the vaccine group, and both of these were in participants over 55 years of age. One death was following a cardiac arrest 62 days after dose two and the other was due to atherosclerotic disease three days after dose one. Neither of these deaths were considered related to the vaccine.

For non-fatal SAEs, these reported -- these included appendicitis in eight vaccine recipients and four placebo recipients. For the vaccine group, two participants were 55 or over 55 years of age and one of these had a perforated appendicitis. None of these events were considered related to vaccination.

One shoulder injury in the same arm as the vaccine administration was reported as an SAE which we attributed as possibly related to the vaccine administration or to the vaccine itself. My next slide here focuses on pregnancy because women were screened for pregnancy prior to each vaccination and were

excluded or not vaccinated if they had a positive result. So as of November 14th, there were 23 pregnancies reported, 12 in the vaccine group and 11 in the placebo group.

The time interval between vaccination as it relates to the date of the woman's last menstrual period are shown here. Two placebo recipients had known pregnancy outcomes, one of which was a spontaneous abortion, and the other was retained product of conception. The pregnancy outcomes are otherwise not known at this time as the pregnancies are ongoing.

Our next slide here shows other safety evaluations. Clinical laboratories commit -- such as hematology and chemistry were assessed in Phase 1 participants. The only common laboratory abnormality reported was a transient decrease in lymphocytes one to three days after dose one, which were mostly grade one to two in severity, and they generally normalized within six to eight days, and did not occur after dose

two.

And among the Phase 1 participants in this study who received the 30 microgram dose, transient decreases in lymphocytes post dose one occurred in 5 of 12 participants in the younger age group, 18 to 55 years of age, and in 4 of 12 participants in the older age group 65 to 85 years of age. These transient hematological changes were not associated with clinical symptoms. Additionally, overall subgroup analyses of the previous safety results were assessed by race, ethnicity, medical comorbidities, and prior SARS-CoV-2 infection without any safety concerns identified by the subgroup analyses.

So in summary, our efficacy conclusions are that the totality of the clinical data submitted with the EUA request meets the expectations for the duration of follow up. In the final S-50 analysis, vaccine efficacy after seven days post dose two was 95 percent in participants without prior evidence of SARS-CoV-2 infection. Efficacy outcomes were consistently greater

than 93 percent across demographic subgroups, and efficacy against severe COVID-19 occurring after the first dose was 88.9 percent. The small number of severe cases is a limitation to these data.

A trend of potential efficacy following a single dose is observed in the data. However, conclusion is limited because almost all participants received a second dose. On our summary for safety here, is that the totality of the clinical data submitted with the EUA request meets the expectations for follow for duration of follow up and evaluation of the All-enrolled population. And this provided additional safety data from a total of greater than 43,000 participants.

Reactogenicity was generally more frequent after dose two in all ages, mostly mild to moderate with less frequency and severity in adults over 55 years of age than in the younger adults. There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical

comorbidities, or prior SARS-CoV-2 infection. As of the data cut off, four cases of Bell's Palsy were reported in vaccine recipients and none in the placebo recipients.

Although there is no clear basis upon which to conclude a causal relationship at this time, we do recommend further surveillance if the vaccine is authorized for widespread use. We're moving on in the outline here. I will move on to the pharmacovigilance plans, future studies, and ongoing study plans.

The sponsor submitted a pharmacovigilance plan to monitor safety concerns that could be associated with the vaccine. The sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. The use in pregnancy and lactation are areas the sponsor identified as missing information.

In addition to the safety concerns specified by the sponsor, FDA is requested that the sponsor update their pharmacovigilance plan to include missing

information in pediatric participants less than 16 years of age, which the applicant agreed to. We also recently requested that the sponsor add anaphylactic reactions including anaphylaxis to the pharmacovigilance plan based on the recent post-market reports of anaphylactic reactions. Next slide is a graphic here to outline pharmacovigilance activities.

AE reporting under the EUA may come from vaccine recipients, vaccination providers, or from the sponsor. First, vaccine recipients will be notified that AEs can be reported to VAERS through the factsheets, or recipients and caregivers. Another source of AE reports from recipients is the V-SAFE program, which is a smart phone based program that uses text messaging and web surveys from the CDC to check in with vaccine recipients for health problems after vaccination. Reports from vaccine recipients are voluntary.

AE reporting by vaccination providers and the sponsor is mandatory. Both the sponsor and vaccine

providers administering the Pfizer-BioNTech COVID-19 vaccine must report to VAERS the following information associated with the vaccine; any vaccine administration errors whether or not associated with an adverse event, serious adverse events irrespective of attribution to the vaccination, cases of multi-system inflammatory syndrome in children and adults, cases of COVID-19 that result in hospitalization or death.

In addition, the applicant will also conduct periodic aggregate review of safety data and submit period safety reports at monthly intervals for FDA review. Each periodic safety report is required to contain a narrative summary and an analysis of adverse events submitted during reporting interval, including interval and cumulative counts by age groups, special populations, i.e., pregnant women, and adverse events of special interest, newly identified safety concerns in the interval and actions taken since the last result because of adverse experience.

Both FDA and CDC will take a collaborative and

complementary approach on reviewing AEs. FDA will individually review all serious adverse events on a daily basis. And FDA will also examine other sources for adverse events such as the literature and will perform data mining to determine if adverse events are disproportionately reporting for the candidate vaccine compared to all other vaccines in VAERS. Any potential safety signals identified will be investigated.

The next slide outlines the sponsor's pharmacovigilance activities that are also included as active surveillance studies, each of which will be conducted over a 30-month time period. The first study will be conducted in a survey of 20,000 healthcare workers. Incident rates of adverse events will be compared to expected rates.

The second study listed will be conducted within the Department of Health, Health System Databases for U.S. military and their families. Rates of adverse events of special interest in vaccine recipients will be compared to unvaccinated

comparators. The final study listed will evaluate for AEs of special interest using the Veteran's Health Administration's electronic medical record database. Vaccine recipients will be compared to unvaccinated participants, or to recipients of the seasonal influenza vaccine.

Moving on. The next slide here will outline the proposed revisions to the study protocol if an EUA is issued. The study design figure shows the current study design, and for participants that originally received the vaccine candidate or for placebo recipients who decline receiving the vaccine under the EUA when it is made available, there is no change to the study design. Participants will continue to be followed as previously proposed through two years post dose two.

The next slide here shows Pfizer's proposal for subjects eligible to receive the vaccine under local and national recommendations at the time of EUA. They can contact their investigator to confirm that

they meet eligibility criteria. They would then be unblinded to know if they received vaccine or placebo. If they received placebo, they would then receive the vaccine within the study conduct and continue with the study for 18 months of follow up.

At visit four -- alternatively, at visit four or six months after dose two, subjects that had not met local or national recommendations for the EUA issuance would then be offered the option to receive the vaccine at that timepoint. And if they accept, both the sponsor and the participant would be unblinded and participants who originally received placebo would then receive vaccine. Participants who cross over from the placebo group to receive the vaccine would then get baseline blood drawn from immunogenicity prior to the first dose, a nasal swab for PCR prior to each dose.

They would then have phone follow up at 1, 6, and 18 months following dose two, as indicated in the figure, in addition to any illnesses for potential COVID-19 symptoms that meet the case definitions. So

the total study duration would still be approximately two years for these participants.

So moving on I will wrap up now with our benefit and risk assessment in the context of the proposed EUA. The known benefits of the vaccine at this time include a reduced risk of confirmed COVID-19 at least seven days after completing a two dose vaccination regimen in individuals without prior history of SARS-CoV-2 infection. Efficacy findings are consistent across subgroups, including racial and ethnic minorities, adults 65 years of age and older, and individuals with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary disease.

Efficacy data in adolescents, 16 and 17 years of age are limited but could be extrapolated from the efficacy observed in adults 18 to 55 years of age. In addition, here is a for our risks. The known risks of the vaccine include local and systemic adverse reactions. In all age groups these were generally mild

to moderate and more frequent following dose two than following dose one. In adults over 55 years of age, they were less frequent and less severe compared to the younger adult age group.

Severe adverse events that were possibly related to the vaccinations included the shoulder injury that we attributed to vaccine administration or to the vaccine itself, and lymphadenopathy that was thought to be temporarily associated and biologically plausible. There are no specific safety concerns identified in analyses of subgroups described or by prior SARS-CoV-2 infection. The data are limited from adolescents 16 and 17 years of age but could be extrapolated from the safety profile in adults 18 to 55 years of age.

The risk assessment is also limited by the duration of follow up at this snapshot in time and the fact that pregnant and breastfeeding women were excluded from the study. In addition, we are aware of the reports of anaphylactic reactions and we are

continuing to collect information to monitor this situation closely. I will now move on to my final slides here to remind the advisory committee of the items that we would like for them to discuss without a vote.

The first of which is that Pfizer has proposed a plan for continuation of blinded placebo controlled follow up in ongoing trials if the vaccine were made available under the EUA. Please discuss Pfizer's plan, including how loss of blinded placebo controlled follow up in ongoing trials should be addressed. The second item to discuss is to discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who would receive the Pfizer-BioNTech vaccine under EUA.

And the final slide here is our questions for the advisory committee to vote on. Based on the totality of the scientific evidence available to the benefit of the Pfizer-BioNTech COVID-19 vaccine both

outweigh its use for risks in individuals 16 years of age and older. With that, I will conclude my presentation and welcome questions. Thank you.

DR. ARNOLD MONTO: Thank you very much. Let's have questions for about 10 minutes or so. We're running late but I think it's critical for us to entertain some questions now. And if anybody I shut off questions to the sponsors so we might want to follow up with questions to the sponsor as well and we can sort it out, the direction of the questions, whether it goes to FDA or to the sponsor. Let's start out with Mr. Toubman.

MR. SHELDON TOUBMAN: Thank you. So I raised this before and that is that the data is now 26 days old, that was the closing date. And I asked a question about, you know, do we have more recent data and Dr. Fink said it hasn't been requested. However, the sponsor is here, and based upon my experience they will have updated data and some other folks may want to ask them about it.

But I have one specific set of data I'd like to ask about in terms of update, probably for them and not for you Dr. Wollersheim, but we'll see. It's about this question is severe disease. And the takeaway -- there's a lot -- I mean, Pfizer suggested it's been demonstrated that their vaccine is effective with severe disease but that's really not the case.

And your conclusion just now was that the case split does suggest protection from severe COVID-19 disease but as stated in your briefing document you just don't have enough data to know that. Well, it's been 26 days, and the question is, do we have such data? All we have based upon what we've -- with the cases 26 days ago, was actually a vaccine efficacy of 66 percent on the actual endpoint, not the other data you talked about which was from dose one. And then you got to 88 percent.

But the actual endpoint that was in the study, and it's been, analyzed came up with a 66 percent vaccine efficacy. And that's concerning the thing that

really matters to me. They care about severe disease. Frankly, almost nobody cares about COVID-19 that all it does is give you a sore throat.

So I think it's really in the public's interest to know what is the story on this vaccine in preventing severe disease, and we really don't have sufficient data to conclude that as of November 14th. So can we get data? Is there data from Pfizer right now, as of yesterday, which shows additional cases that gives us more data such that we can actually -- they conclude in their document that the data does not meet prescribed (inaudible) criteria, the endpoint of severe disease?

Maybe that new data does. And then the second question is, if it's not sufficient yet, at what point do we project we might have sufficient data so we could really look at that critical question of, does this vaccine really prevent severe disease?

DR. ARNOLD MONTO: Could I ask the Pfizer team to respond about additional data?

DR. KATHRIN JANSEN: -- comes to the relevance. I'd like Dr. Gruber to respond to the first question in terms of additional data. And then also when it comes to severe disease, I would like to invite Dr. Stephen Thomas to give his perspective of the medical importance of preventing --

DR. ARNOLD MONTO: We really need to keep this -- we need to keep it brief.

DR. KATHRIN JANSEN: Alright. Just Bill then.

DR. ARNOLD MONTO: Okay. Just --

DR. WILLIAM GRUBER: Yeah. I can be fairly brief here.

DR. KATHRIN JANSEN: Go ahead.

DR. WILLIAM GRUBER: The answer to the question as we heard earlier, it takes quite a bit of work to essentially prepare a data package for comprehensive review by the FDA. So since November the 14th we obviously have not done the additional unblinded analysis. We will do that obviously at the direction of the FDA.

And there is obviously potential over time at an appropriate time in collaboration with the FDA to look at that again. I can tell you that we don't have enough additional cases post second dose to greatly enlarge that data. But I would emphasize that the data where we see the 1 to 9 split using the FDA guidance after the first dose and the 1 to 14 split, I think in my view, and it seems to be in the FDA's view, is compelling for evidence of protection. I think it's just a matter of getting enough cases and we have the potential to have more cases over time but we've not analyzed those yet. Everything --

DR. ARNOLD MONTO: Dr. Wollersheim, anything to add?

DR. SUSAN WOLLERSHEIM: No. I agree. At some point, I guess we'll have those discussions in terms of when additional data will be requested but that's not the topic for today's EUA discussion.

DR. ARNOLD MONTO: Okay. Let's go on to --

MR. SHELDON TOUBMAN: If I could follow up --

DR. ARNOLD MONTO: No follow ups. We -- we're pressed for time. I got 10 people who want to talk -- ask questions. Dr. Kurilla.

DR. MICHAEL KURILLA: Yeah. I've got -- I'd like FDA to make two comments. One, with the clinical findings of loss of smell and taste which also involved cranial nerves, is Bell's Palsy that odd in your mind that it could not be associated with some immunological response to the antigen? And the second is, in looking at the data package, we don't as yet have a recognized or accepted correlative protection.

And the panel of human convalescent plasma, if I recall it was derived from 38 individuals, 35 of which had mild disease. Only one was hospitalized. I'm assuming the other two were asymptomatic. But we know that the antibody titers do scale with the severity of infection.

So it seems like a little bit of a low bar to be comparing against people who had mild disease who may be mediating other innate immune responses. And so

I'm just trying to get a sense of who we can move forward following people who get vaccinated when we don't really have a recognized correlative protection. And then for the Pfizer group, the question I wanted to ask before is, you have tripled in terms of innate immune responses of the vaccine, but is that in general innate immune responses, or is that related specifically to Toll-like receptor responses?

Given that the younger individuals had more reactogenicity, it sounds more inflammatory. And I wonder if generation of interferon responses and potentially natural killer responses from the vaccination and antigen non-independent response, or an antigen period? And since you're period of time for overall efficacy is very short are you actually not measuring the true efficacy of your adaptive immune response that you are clearly generating?

DR. ARNOLD MONTO: Dr. Wollersheim, please. Responses kind of brief. Okay? Dr. Wollersheim first.

DR. SUSAN WOLLERSHEIM: Sure. Thank you. I

think your first question is regarding causality with Bell's Palsy and just given the small numbers of cases that we have it would be difficult to attribute causation at this time. I do see correlating potential, but I think that this is unclear at this time to attribute to the vaccine. And your second question was regarding comparison of GMTs to the convalescent plasma panel. I do see your point with the symptomology comparison of correlating potential, of GMTs to the convalescent plasma panel.

And I might actually ask Pfizer to address this question because I know that they had two different panels of convalescent plasma that they (audio skip) data and I don't recall off the top of my head which one was used in today's presentation, and what the composition of those patients that submitted to those panels were. So I will actually let Pfizer address that question, please.

DR. KATHRIN JANSEN: Yeah. If it's okay I can answer this. So it was a panel of 38 (audio skip)

they were collected 14 days after PCR confirmed COVID-19 case at a time when the donors were asymptomatic. We had 35 symptomatic infections. In that, three asymptomatic infections, one individual was hospitalized. And we -- I just want to stress that we used that panel initially to give us guidance of how a vaccine-induced immune response compares to a panel of individuals that had contracted COVID-19. We did not use that to make any decisions or draw any conclusion in terms of a correlate of protection.

DR. ARNOLD MONTO: Okay. We're going to not worry about adaptive and innate immune responses right now. We'll take that off-line. Dr. Perlman, your question.

DR. STANLEY PERLMAN: Yeah. Yeah. Okay. Yes. I just had a question about pregnant women, because if an EUA is of pregnant women not being immunized but we have no data --

DR. SUSAN WOLLERSHEIM: I will defer that question here to Dr. Fink who is here.

DR. DORAN FINK: Hi. Thanks for asking that question. I'm trying to activate my video but the --

DR. ARNOLD MONTO: We know what you look like, Doran.

DR. DORAN FINK: Alright. So in the --

DR. ARNOLD MONTO: Let's go ahead.

DR. DORAN FINK: -- interest of time -- right. So in the interest of time. You are correct that we have very limited data on the use on pregnancy. We are expecting results of a developmental and reproductive toxicity study in animals to be submitted to us later this month. That type of data typically precedes licensure of a vaccine.

In terms of inclusion of pregnant women in the EUA, we recognize that among the groups first prioritized for vaccine use under EUA there will be many women of childbearing potential including women who are pregnant, either knowingly or unknowingly. And we have really no data to speak to risks specific to the pregnant woman or the fetus, but also no data that

would warrant a contraindication to use in pregnancy at this time.

And so in the interest of allowing women of childbearing potential who would consider vaccination to be right for them, we could consider including them in the EUA population -- the population approved for use under EUA. They would be then free to make their own decision in conjunction with their healthcare provider.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer.

DR. MARK SAWYER: Thanks very much and I'd like to thank all the presenters and all the many, many people who contributed the work to the presentations. My question is for FDA and it is about the 16 to 17 year old group. I am concerned about the lack of data, particularly reactogenicity, and I'm not aware of any other vaccine where we've interpreted or extrapolated adult data down into the adolescent years.

I appreciate that 16 and 17-year-olds are big and hairy and pretty close to adults, but they're not

exactly the same. And so my specific question is, if this data holds six months from now and there's no safety concern and we have this level of evidence of effectiveness, one case in a placebo group and no cases in the vaccine group, would that be sufficient for a BLA to be down to the age of 16? Thanks.

DR. WILLIAM GRUBER: Maybe I can --

DR. KATHRIN JANSEN: Yeah. I'm not --

DR. WILLIAM GRUBER: -- that question. So that's a decision that we would have to make at the time that we are considering a licensure application. Our regulations and laws do allow us to extrapolate effectiveness and safety from adult populations into pediatric populations as you mentioned. The ages of 16 and 17 are those adolescents that are closest in age to adults and so the extrapolation becomes biologically all that more reasonable.

As well, 16 and 17-year-olds are at increasing risk of exposure to SARS-CoV-2 because of activities that they typically engage in. So as outlined in Dr.

Wollersheim's presentation, for the purpose of this EUA we do consider that safety and effectiveness from adults, in particular younger adults, could be extrapolated to older adolescents ages 16 and 17.

DR. ARNOLD MONTO: Thank you. The last question that we have time for right now before we have a very short break is from Dr. Rubin. Please.

DR. ERIC RUBIN: Thank you for your -- thank you for your careful analysis. It gets to one of the post hoc analyses you did. It looks as if 19 participants regardless of their -- whether they were placebo or vaccine recipients got -- developed disease within the first 28 days. If you calculate that rate, play with the numbers as much as we have them, that's a pretty high rate of infection. It's actually a little higher than the rate in the group that was allegedly not immune.

And I wonder if that brings into question whether or not the anti-nucleic acid antibody is actually a very good test because there's a lot of

independent evidence suggesting that people with anti-spike protein antibody have -- are relatively protected. Since the entire evaluation of asymptomatic disease is going to depend on that, I wonder if the test is any good.

DR. SUSAN WOLLERSHEIM: That's a good question and at this point those antibody tests have been qualified for that stage of development. It's not part of their final analysis at this point so they've not been validated to a certain extent. So that would be something that we will be discussing further.

DR. ARNOLD MONTO: Right. And there's also the issue of seasonal Coronaviruses.

DR. SUSAN WOLLERSHEIM: Yes.

DR. ARNOLD MONTO: When you get into --

DR. SUSAN WOLLERSHEIM: I would give Pfizer the opportunity to address the assays as well if they wish.

DR. ARNOLD MONTO: Pfizer representative please and we'll call it -- then we're going to take a

break.

DR. KATHRIN JANSEN: Yes. Sorry. I was on mute. Yes. So we have used the N-protein assay to distinguish it from a vaccine in dose response. But we need to demonstrate a prevention of asymptomatic infection and we can't use the spike protein for this purpose because, you know, otherwise everyone would be positive that received the vaccine. The second question I believe that you were asking I'm blanking right now was -- the second part of your question --

DR. ERIC RUBIN: Well, it was whether it was really -- whether it was a good correlate of prior infection, the N-protein.

DR. KATHRIN JANSEN: Yes. So it is our understanding that N-protein positivity does indeed develop within probably two weeks after becoming infected. There's of course another way to determining infection, which is by more frequent sampling using PCR. Both are I think valid approaches from our perspective.

In terms of cross-reactivity with other seasonal Coronavirus, it was very important to demonstrate it. So we have carefully looked at the N-protein assay that we are using. It's a commercial test. And have evaluated a relatively large number of sera that were collected prior to the appearance of SARS-CoV-2 and we have not seen any evidence of cross-reactivity to seasonal Coronaviruses.

DR. ARNOLD MONTO: Okay. Well, let us now take a -- looking at the clock, a break until 10 minutes to four. Hard start at 10 minutes to four. The meeting on October 22nd went on until a quarter to seven eastern and I don't think we want to go on that late tonight.

MR. MICHAEL KAWCZYNSKI: Alright. With that, we're going to take a break.

[BREAK]

COMMITTEE DISCUSSION AND VOTING

MR. MICHAEL KAWCZYNSKI: All right. Welcome back and we are now ready to start our Committee discussion. So with that, Dr. Monto, would you like to take it away?

DR. ARNOLD MONTO: Right. And I guess there we are. Could you put the discussion questions up, please, Mike?

MR. MICHAEL KAWCZYNSKI: Yes, I just did, sir.

DR. ARNOLD MONTO: All right. I don't see them yet.

MR. MICHAEL KAWCZYNSKI: It may take a moment as you just came in. Just give it a moment, sir.

DR. ARNOLD MONTO: Okay. Let's discuss what we're going to do in the discussion. Because I've had to cut off questions that were going to be addressed to the presenters, the sponsor and FDA. What I would suggest, since we are running quite late, is that we have a discussion of these two items and ask the

sponsor and FDA, as we go through, of any items of fact that they can help us in this discussion. So I don't need to read to you the discussion items.

Item one is please discuss Pfizer's plan, including how loss of blinded placebo-controlled follow-up in ongoing trials should be addressed. So we're talking here about plans for giving dose three and dose four as was shown in the last presentation. And also gaps in plans described today for further evaluation of vaccine safety and effectiveness.

So I think they're related, and I think we need to continue our discussion around both of these points, plus any other specific questions you have of the sponsors or FDA. I think we want to stay away from more discussions about immune response and other things that could be taken offline. So with that introduction, Dr. Gans?

DR. HAYLEY GANS: I had a question regarding the unblinding, if we go through with the EUA as number one. The actual unblinding in any manner -- so if we

did the crossover -- how is that actually going to affect the BLA? Because all of the data that was presented today on how they would move forward on the BLA is assuming that there isn't an unblinding (audio distortion). So I think that would be important for us to understand the impact it's having on an EUA. And my follow up question (audio skip) because I think we've seen a lot of conversations --

DR. ARNOLD MONTO: You're breaking up. Are other people able to hear?

MR. MICHAEL KAWCZYNSKI: No, she is breaking up a little bit, Dr. Gans.

DR. HAYLEY GANS: Sorry about that. Is this better? Hello?

MR. MICHAEL KAWCZYNSKI: Go ahead. Continue.

DR. HAYLEY GANS: Okay. My second question was we had a lot of questions about the use of the vaccine and, as we've heard, a systemic -- continued -- that would be to asymptomatic (inaudible) and therefore being contagious to those outlets. And it would be

very important to understand even if they had any data from Health (inaudible) in terms of people who're already vaccinated at the rates (inaudible) situation.

DR. ARNOLD MONTO: Let's keep the second part of your question, which we had problems hearing anyway, to the discussion before we get to the voting question. Because we're going to want to have a second round of discussions before we get to the voting question. So is there anybody from FDA who wants to address the issue of how the unblinding issue could affect the BLA?

MR. MICHAEL KAWCZYNSKI: Anyone? Dr. Gruber? Dr. Gruber, let's just make sure that we unmute you. There we go.

DR. MARION GRUBER: I know. It took me a minute. I just wanted to say that starting with a general comment that, of course, the gold standard for doing phase 3 studies to demonstrate the safety and the efficacy of a product is by randomized controlled trial, ideally the placebo-controlled study. And this is why, from a regulatory perspective, of course, we

would welcome continuing the placebo-controlled follow up for as long as feasible, recognizing the complexities thereof. And that was, I think, very nicely discussed by Dr. Goodman this morning.

So we would of course be looking at potentially losing longer term safety follow up. But realizing the gravity of the pandemic, and if we really looking at having to think about other designs and modifications of the protocol, we would be looking at that and to see and make sure that we have sufficient data regarding safety. I'm not that worried about effectiveness, but regarding safety then to support the BLA application. So, I think, if it's no longer feasible to really keep the blind -- to really get those data from a placebo-controlled efficacy study, we would, of course, look at other approaches to get these data. And I'll stop it here and, I think, perhaps Dr. Fink wants to add to that.

DR. DORAN FINK: I actually don't have much to add. I was trying to jump in, and the platform wasn't

letting me. It seems to be a delay, so nothing more.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Fuller? And let's try to keep to one-part questions until we catch up at least. Dr. Fuller?

DR. OVETA FULLER: Yes, thank you. This is a simple question. Risk assessment is going to be very critical for uptake of the community. Was the placebo including the LNT, or did it only have other materials? So in other words, are the side effects that we've seen in the limited amount of risk assessment, that's been done in two months, due to only the spiked protein because the placebo has the lipid material? Or is that due to both the lipid and the spiked protein expression and we don't know what the lipid does alone? This will be really critical considering that most of the people who are getting vaccinated have not yet seen multiple exposures to the coronavirus. So what does that mean for long-term effects that cannot even be looked at right now because we just got this into people?

DR. ARNOLD MONTO: Okay. I don't know who

wants to take that. Dr. Krause?

DR. PHILIP KRAUSE: Just to answer quickly, the placebo control was a saline control, so the vaccine is being compared against a complete placebo, not against the lipid. So the side effects that were observed are due to the combination of the lipid and the mRNA.

DR. ARNOLD MONTO: Okay.

DR. OVETA FULLER: So we have no idea what putting a messenger RNA lipid vaccine into people does long term? It's not been done before. And we're going from 20,000 people who get this vaccine to millions who get this vaccine, with a very limited amount of risk assessment. Is that correct?

DR. ARNOLD MONTO: Dr. Krause?

DR. PHILIP KRAUSE: I apologize. I'd accidentally muted you when I was trying to get off here, and so I did not hear that question.

DR. ARNOLD MONTO: A limited database.

DR. OVETA FULLER: Yes, we have very little

information about what happens to people who get the vaccine, and then subsequently get exposed to COVID-19. Because we've only looked for two months, and that didn't include -- it included the vaccine with a lipid and the messenger RNA. So we don't even know what's going to happen long-term to people who get these lipid particles plus the vaccine. There's such a limited risk assessment that I think the uptake in the community is going to be fairly poor unless something better is done.

DR. PHILIP KRAUSE: Pfizer may comment, but there has been a number of other vaccines, that have been mRNA vaccines, that have been studied where people have gotten these lipids and have been followed for considerably longer periods of time. Although, not the very large numbers of people that you might be looking for here. But perhaps we can give Pfizer an opportunity to comment on that.

DR. OVETA FULLER: Also, we know that COVID-19 is a multi-organ disease, so it's not like some of the

previous lipid vaccines.

DR. PHILIP KRAUSE: Yup.

DR. OVETA FULLER: This is something we don't know very much about the pathology of this coronavirus.

DR. ARNOLD MONTO: Dr. Jansen and then we'll move on, please. I think you're muted.

DR. KATHRIN JANSEN: We actually have evaluated what happens after -- when individuals are being exposed by COVID-19 in our last study. So while we have relatively few cases of individuals that had (inaudible) interactions with COVID-19, nevertheless, those individuals showed, as we saw, a much lower profile of severity comparing to the many other -- the 162 individuals that received placebo.

The other point I would make, is that we have stated multiple times that we will follow our trial participants up to the end of the study, which is planned to last for the full duration of 24 months.

DR. ARNOLD MONTO: Thank you.

DR. OVETA FULLER: Thank you.

DR. ARNOLD MONTO: Dr. Offit?

DR. PAUL OFFIT: Okay. Thanks. My question is for Bill from Pfizer. I'm worried about the severe anaphylactic reactions for this reason. We don't know the details of those two cases. We don't know specifically what it was they were allergic to or what their history with severe allergies was, we just know that they carried EpiPens. The public health people in the UK said if you had a history of severe allergies, you can't get this vaccine. Similarly, Moncef Slaoui here, head of Warp-Speed, said the same thing. If you have a history of severe allergies, you can't get this vaccine.

There are tens of millions of people in this country who carry EpiPens with them -- because they have peanut allergies, because they have egg allergies -- who are going to believe now that they can't get this vaccine. That's a lot of people.

So what I would suggest is first we need to drill down on those two people in the UK. But I think

more importantly, Dr. Gruber, you had said that there were no cases of severe allergy in your trial. Did you exclude people with a history of severe allergy? That's question one.

DR. WILLIAM GRUBER: Let me address question one, and then I think maybe what I'll do, Dr. Offit, is defer to our head of safety at Pfizer who can describe more about what we know about the cases that occurred in the UK and then the nature of our plans for moving forward. And perhaps we can even include the regulatory view.

So the nature of what was actually excluded from the trial was really restricted to those individuals who had had a severe allergic reaction to a vaccine -- any vaccine previously. Or if, obviously, during the course of the trial they'd gotten the first dose and they had a significant type 1 hypersensitivity response, then that would preclude giving a second dose. And we did not encounter that circumstance in the trial.

The first circumstance, I don't know how many people we actually screened out who'd had a prior issue with having had an anaphylactic reaction to a vaccine, but we didn't have to exclude anybody from getting the second dose. So as I said, at least during the course of the trial, we have not seen anything that alerted us to a safety signal associated with the vaccine or potential for anaphylaxis. But maybe what I can do is -- yeah. Go ahead.

DR. PAUL OFFIT: So Bill, what I'm asking is this. Do you know whether there were people in the trial who were in the vaccine group who had a history of severe anaphylaxis, period, not necessarily to a vaccine. Or if they had a history of carrying an EpiPen? Do you have those data?

DR. WILLIAM GRUBER: Yeah. Let me ask Dr. Caubel to share with you what we do know in terms of the nature of pre-existing allergic conditions and the outcomes in the trial. To my knowledge, we didn't have anybody that had had a prior history of anaphylaxis.

But let me ask Dr. Caubel to actually share with you the information that we do have.

DR. PATRICK CAUBEL: Good afternoon. I'm Dr. Patrick Caubel. I'm the head of safety here for Pfizer and also the Chief Safety Officer for Pfizer. Actually, we know more about these two cases that occurred in the UK, so let me give you more detail about these two cases.

So these two cases, in fact, were reported in the UK from December 8, so which means -- because they have the vaccination campaign in the UK. So the same day, 6,000 people were vaccinated, and all these vaccinations were performed in hospital settings because the primary target for the vaccination in the UK are healthcare providers. In fact, it happened that these two subjects were not only -- as I say, healthcare workers, they were 49 and 40 years old. The first subject, in fact, had a medical history of serious allergic reactions, so he had a severe allergic reaction with anaphylaxis.

But not following drugs, she had, in fact, food allergy with allergy to eggs and to cheesecake and lemon and lime. But in fact, the last episode of the cheesecake led her to the emergency room where she needed to have resuscitation and administration of epinephrine. So in fact for research patients of the case of anaphylaxis occurred only two minutes after the vaccination. She required an administration of epinephrine, corticosteroids, and finally the patient fully recovered.

The second patient, in fact, was a little bit milder, but it was a patient who also had a medical history of allergy to drugs. We don't which drug yet, but she was under the care of an immunologist before receiving the vaccination. So it was mostly, in this case, shortness of breath, (inaudible), and finally she required also the administration of epinephrine.

Again, these two cases occurred the first day of vaccination. We have also a third case that was reported the second day of vaccination, which was not

really a case of anaphylaxis. It was just a patient who developed a (inaudible). She had some skin redness. She was given (inaudible) and antihistamines, and then she went back into a similar mode and finally also fully recovered. At this stage, we don't think that this case developed (inaudible).

DR. PAUL OFFIT: Can I ask Dr. Gruber how FDA is going to respond to these reports?

DR. PATRICK CAUBEL: Do you want to answer or --

DR. ARNOLD MONTO: I think he was speaking of Marion Gruber. I think this is the FDA --

DR. PAUL OFFIT: I was speaking of Marion Gruber.

DR. MARION GRUBER: Okay. I just also wanted to say I am not aware that we are related, Bill, so we had that discussion before. So yeah. So first of all, we have been in communication with the Medical Healthcare Products regulatory Agency, MHRA, in the United Kingdom who made us aware of these two cases of

anaphylactic reactions. And what was just reported about what is known about these was also transmitted to us.

At this point, we are seeking further information from the MHRA under our confidentiality agreement to learn more about this and to really tease that out. I also wanted to remind the Committee -- and I think Dr. Wollersheim really presented that nicely -- of the safety analysis that the FDA independently conducted by doing standard medical queries. And we looked at events that could potentially include or present allergic reactions. We found a slight numerical imbalance there that Susan reported and presented on.

I want to stress that none of these were considered to be serious. None of them received epinephrine injections, and none of these events occurred in the immediate post-vaccination period. That being said, over the last couple of weeks, we have been working with Pfizer on generating fact sheets and

prescribing information.

And we -- FDA and the sponsor -- we agreed for the fact sheets and the prescribing information for this vaccine to include information under contraindications and under warnings. So the fact sheets and the prescribing information will state that this vaccine should not be administered to individuals with known history of severe allergic reactions to any components of Pfizer's COVID-19 vaccine. And the warning statement will say, appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Pfizer COVID-19 vaccine.

So that has made it already in these fact sheets and prescribing information weeks ago. We, however, will consider any additional information that we're going to be receiving over the next couple of days, and factoring this into our decision making to decide whether the fact sheets and the prescribing

information may need to be further revised to include additional precautionary statements. And I'll leave it here. Thank you.

DR. PAUL OFFIT: Marion, could I just offer one thing and then I'll stop? If you look at the components of that vaccine, which has probably the longest chemical name of any vaccine I've ever seen in terms of that lipid, nobody's going to look at that name and think, you know, I'm allergic to that.

So here's what I would suggest, moving forward, just as a practical solution. I think a study should be done by Pfizer or whomever where you take people who have a known history of severe egg allergy, a known history of severe peanut allergy and given them these vaccines under careful observation to prove that this is not going to be a problem for them. Because you're talking about tens of millions of people who are going to not get this vaccine because of the comments that were made both by the UK and both by Moncef Slaoui here. I just think it's a practical solution because

this issue is not going to die until we have better data.

DR. ARNOLD MONTO: Okay. Let's -- Marion, do you have anything to add? And then we'll go to Dr. Meissner.

DR. MARION GRUBER: Yeah. Just in response to that, I hear your suggestion, Paul, and I think so did Pfizer. We, however, need to decide on the issuance of an EUA the next couple of weeks and/or days -- days more than weeks. And we are looking at the question whether the benefits outweigh the risks, you know --

DR. PAUL OFFIT: I agree. The benefits -- I mean, I'm fine with that.

DR. MARION GRUBER: -- not determine if this product is safe and effective for the purpose of licensing it. I just wanted to remind you that.

DR. PAUL OFFIT: I agree.

DR. MARION GRUBER: Thank you.

DR. ARNOLD MONTO: Okay. Let's move on to Dr. Meissner. You're muted.

DR. CODY MEISSNER: First of all, in terms of our current discussion of anaphylaxis, remember that's recommended for any vaccine that's administered. The vaccinator should be able to handle anaphylactic reaction from any vaccine. It wouldn't be just for a COVID-19 vaccine, number one. And, Paul, I'm not sure that an allergic reaction to ovalbumin would have much bearing on the risk of a reaction to this vaccine.

Number two, going back to the pregnancy discussion, my concern is that during pregnancy there's a great deal of replication, of DNA replication, cellular replication that's occurring in the fetus. And vaccinating a pregnant woman with this messenger RNA gives me a little bit of pause. We certainly -- and I understand the response, but could there be a retrovirus somehow around -- a migrant retrovirus and reverse transcribe this RNA into the chromosome of the baby? That is one thought.

The next point, I agree very much with Dr. Mark Sawyer in his comment about a 16- and 17-year-old.

There are only 163 subjects who have been enrolled in the randomized trial, and we have heard that the inflammatory response is higher in younger people than it is in the elderly. I think we need more information before we think about that.

And then the final point I want to make -- and thank you for your patience -- back to Dr. Gans, it's so important -- an EUA -- we need this vaccine. We need to do our very best to develop herd immunity. We need this vaccine. But we need to move it from an EUA to a BLA as soon as it satisfies the threshold that the FDA will hold this vaccine to. But there are many reasons to move it to a BLA, such as it will be included in the vaccine injury compensation program if the CDC recommends it for adults and for children. So I think we need to move in that direction. Thank you.

DR. PAUL OFFIT: Cody, I just want to say one thing. I'm not talking -- I completely agree with you, but I don't think --

DR. ARNOLD MONTO: Very quickly.

DR. PAUL OFFIT: Okay. Quickly. I just think that I'm talking about perception more than reality. With those two statements out there -- that people who have severe allergic reactions shouldn't get this vaccine -- I think we just need to offer people some solace that this is not going to be a problem for them.

I'm not saying this should stop us moving forward at all with approving this vaccine. I'm just saying, when it rolls out there, this is going to be an issue, and we need to have some data that we arm ourselves with so we can address it. That's all. I'm not saying it's biologically sound. I'm just saying that we need data to argue against -- any more than vaccines cause autism was biologically sound. We just need data to address it. That's all I'm saying.

DR. CODY MEISSNER: I agree.

DR. ARNOLD MONTO: Thank you. I think we agree, perception is everything. Facts may be important, but perception drives a lot of decisions. Dr. Annunziato?

DR. PAULA ANNUNZIATO: Thank you. I have a question for Dr. Bill Gruber. Bill, in your study can you describe for us how the non-solicited adverse experiences that were collected up until one month after dose two were collected? In other words, was there active surveillance for those events as well?

And then for your plans for under an EUA, if a subject is unblinded and vaccinated, could you also just reiterate for us what safety surveillance you will be conducting in that situation?

DR. WILLIAM GRUBER: Yes, thanks, Paula. I may call upon Nick Kitchin to help with some of the details. He's the clinical lead for the program. But the e-diary information was solicited and collected for the first seven days, and then investigators were encouraged to potentially collect adverse events but in an unsolicited fashion for the first month after administration. And then, I'm sorry, the second question was what, again?

DR. PAULA ANNUNZIATO: Was what are the plans

for safety collection for the subjects who may opt to be unblinded and then vaccinated after the EUA is issued?

DR. WILLIAM GRUBER: Right. So I'm going to defer to Dr. Kitchin who's helped put together our latest amendment that deals with management of the placebo recipients to address both questions, but particularly the second one. Dr. Kitchin?

DR. NICHOLAS KITCHIN: Thank you, Bill. This is Nick Kitchin from Pfizer. Can you hear me okay?

DR. PAULA ANNUNZIATO: Yes.

DR. NICHOLAS KITCHIN: Okay. Yeah. So with respect to elicitation of adverse events and specifically the reactogenicity type events that you were asking about for subjects that were not in the subset, they were elicited in the same way as other adverse events. There weren't specific leading or directed questions to elicit specifically for those events, and that's why you typically would expect to see them -- seen at a lower rate when reported as

adverse events rather than when it's actively solicited daily for seven days immediately after vaccination in the diary. So for reactogenicity, the data from the subset gives us the best picture of the profile.

With respect to our plans for safety surveillance for subjects that would be receiving the BNT162b2 as a result of being eligible, for example, under EUA, our intention is to use the same safety surveillance as those not in the subset. So we would not use e-diaries for those subjects that were moving across, but they would have all adverse events elicited for one month after what would be their fourth vaccination but their second active dose and six months post previous adverse.

DR. WILLIAM GRUBER: I might just add, Paula, as you can well recognize, 8,000 subjects set for common events that are being solicited routinely like fever, headache, fatigue, the chills. We probably have -- in fact, I'd argue we do have -- sufficient precision on those common sorts of events. So it makes

less sense, I think, to essentially say come back and to also now have to essentially do the e-diaries again. I don't think it really will add value, and it potentially could mitigate against individuals wanting to participate.

DR. PAULA ANNUNZIATO: Sure. Thank you.

DR. ARNOLD MONTO: Dr. Lee?

DR. JEANNETTE LEE: So my question is really for Pfizer about their blinded follow up, or unblinding the placebo recipients. And I think one question I have is why in your unblinding is there not incorporated some sort of scale, or whatever you want to call, for severity, rare, or risk factor either based on age, co-morbidity or so forth? Instead, you're relying on local and national guidelines, and I can tell you they're going to vary state by state, county by county here. And you're going to have a hodge-podge. So it seems if you were going to incorporate something about the risk factors, you might have a little bit more consistency on the follow up for

various risk groups. And I didn't know if Pfizer had considered that at all.

DR. ARNOLD MONTO: I'm glad you asked this question because it moves us back to the discussion topic. Can we have Pfizer respond please?

DR. KATHRIN JANSEN: Yes, could I please ask Dr. Anezden (phonetic) to explain in detail how we are going to follow vaccine recipients over time?

DR. JEANNETTE LEE: No, it wasn't a question of follow up. It was a question of identifying when somebody would be eligible to be unblinded that would include their risk factors, not just local and national criteria because they will vary tremendously in this country and I suspect elsewhere.

DR. KATHRIN JANSEN: Okay. That may be Dr. Gruber. Please continue.

DR. WILLIAM GRUBER: Yeah. And again, I may call upon Nick to help with this, too. We obviously -- as you heard this morning from Dr. Goodman, this is an incredibly challenging area for us to put forward the

right path. We want to be contentious about providing vaccine to individuals who would qualify. So the onus is on us to take the emergency use authorization and the recommendations to heart. If you happen to live in an area where in fact you are eligible, we'd be hard pressed to say, "Well, because we've taken a national recommendation, you don't fit because we're just going by the national recommendation."

I think we have yet to see how that will work in practice, but it is our intent to try to do what we think is right to follow the guidance and local recommendation. We're also, obviously, facing this issue, as you can perceive, not just on a national level but internationally since we have a number of countries involved. So we have to look at each of those issues and weigh them to make that type of decision. I don't know, Nick, if you have anything else to add to that.

DR. ARNOLD MONTO: I know that you will be in discussion, Bill, with FDA about these as well.

DR. WILLIAM GRUBER: Right. Right. I mean, that's clearly, in part, why I'm glad this is a topic for discussion.

DR. ARNOLD MONTO: Exactly.

DR. NICHOLAS KITCHIN: Sorry, Bill. Yeah. This is Nick Kitchin again from Pfizer just to add. So yes, our intention, at least initially, we would anticipate in terms of the recommendations following the initial ACIP recommendations. So we will provide specific guidance -- more specific than applying to local and national recommendations. But certainly to start with, I imagine, it would follow how ACIP would recommend allocation of the initial doses.

DR. ARNOLD MONTO: Thank you. And as we go forward, please mainly pay attention to the discussion items because, as many have stated, we'd like to move to a BLA submission promptly or as smoothly -- I won't say promptly -- as smoothly as possible. And the answer to some of these issues is going to affect that. So Dr. Moore?

DR. PATRICK MOORE: Hi, yes. One question that addresses these two discussion items, I find is really, really central, and important, is that FDA did not ask in its guidance and Pfizer has presented no evidence in its data today that the vaccine has any effect on virus carriage or shedding, which is the fundamental basis for herd immunity. And so even though the individual efficacy of this vaccine is very, very, very high, we really, as of right now, do not have any evidence that it will have an impact, social-wide, on the epidemic.

So I would like to ask, before the unblinding, that Pfizer seriously consider performing nucleic acid assays on the vaccinees and the placebo patients. I don't know whether the point estimate for shedding is going to be high enough that you're going to see a significant difference, but at least one should try because that's one piece of data that we're going to completely lose once the unblinding occurs.

DR. ARNOLD MONTO: Let me just interrupt and

tell you that these questions are being addressed by CDC in the observational studies as we go forward, because of sample size issues and a lot of issues that are not possible when you're not looking at households where transmission will take place.

DR. PATRICK MOORE: Right. And with the CDC, they certainly would like to have a toe-in to the vaccine companies to be able to help perform these very types of studies if at all possible. And so that industry-CDC collaboration would be tremendous. But it is so important as of right now as to whether or not this vaccine can have an impact on the non-vaccinated persons who are at risks for acquiring infection. We don't know that.

DR. ARNOLD MONTO: Dr. Jansen, you want to comment?

DR. KATHRIN JANSEN: Yes, we actually are looking into this to do precisely that. Not just to look for prevention of asymptomatic infection but also doing the PCR testing to look for virus equation -- or

prevention of virus acquisition.

I may remind, though, that we have data, not from humans but from or non-human primate study, that would argue that the vaccine does prevent infection. We have seen that it prevents infection of the lung, and we have also seen some evidence that it has a more transient -- that the virus is more transiently detected in the vaccinated animals compared to the control animals.

DR. ARNOLD MONTO: Okay. We're going to have move on. Dr. Kim?

DR. DAVID KIM: I think this relates to discussion item number two. Vaccine efficacy data might not be evident for HIV positive study participants given they're small number, but presumably preliminary vaccine safety data are available. After all, trial participants were enrolled in October, and EUA application was made on November 20. Would Pfizer please comment are there any updated information, since people with HIV infection, or other conditions that are

stable and meet the criteria for vaccination, will be standing in line for the vaccine in short time?

DR. KATHRIN JANSEN: Bill, could you please comment?

DR. WILLIAM GRUBER: Yeah. So obviously, we included individuals, as I mentioned and Dr. Jansen mentioned, with HIV, HCV, and HBV if they had stable infection. And we included additional evaluation beyond the core group that we're looking for solicited, non-solicited adverse events. So within the population that we have so far, we have -- within the 38k database -- about 120 of these and 196 in the total 43,000-plus database.

So we're getting to a point where we will have enough of those individuals to look at, and we would propose, obviously, doing that in association with the filing that goes into BLA, if not sooner. We just need to have enough of them. As you may know, we amended the protocol in flight, so there was a little bit of delay. That was really the only population apart from

the 12- to 15-year-olds that were a little bit delayed in terms of enrollment in the trial because of the way that was staggered. But yes, it is our intent to essentially have more information on that population.

DR. ARNOLD MONTO: Okay. Dr. Pergam?

DR. STEVEN PERGAM: Thanks. So I had a question about since this vaccine is going to be rolled out through the EUA, there's going to be a fair number of people who might have access the vaccine who've had previous COVID exposure, may not know they've been positive, or have known history of positivity. There's limited data in the trial, at least, because of enrollment, for people that are previously positive.

Two questions kind of relating to both of these things is, thinking about potentially looking at side effects within the group that potentially gets this, is there an increase enhancement of the side effects? It didn't look like it in the initial data you showed.

But looking at that a little more carefully in

people that have known prior positivity. And then secondarily, I'm curious what are you going to do with patients in the clinical trial who did develop COVID? Are they going to also be offered the vaccine, just as a question for Pfizer?

DR. ARNOLD MONTO: Dr. Jansen, I think you're muted.

DR. KATHRIN JANSEN: I'm sorry. Can you hear me now?

DR. ARNOLD MONTO: Yes.

MR. MICHAEL KAWCZYNSKI: Yes, we can hear you Kathrin.

DR. KATHRIN JANSEN: Yeah. So I think we may have lost the link.

DR. ARNOLD MONTO: No, we can hear you.

DR. KATHRIN JANSEN: Oh, you now can? Oh, good. Okay. Thank you. I would like to take the first part of the question and then have Dr. Gruber comment on the second one. So while we have excluded individuals with known COVID-19 -- so meaning PCR

confirmed COVID-19 -- we actually do have in our trial individuals that are seropositive. In other words, they were prior exposed to COVID-19. And so our estimate is about 2 to 3 percent of the individuals who are participating in our trials were seropositive at baseline. Bill, if you want to take the second?

DR. WILLIAM GRUBER: I think the second question was about the nature of the safety profile in individuals that had evidence of a prior SARS-coronavirus infection or were PCR positive at the time they adhered to their first or second dose. And the bottom line is -- and this has been submitted to the FDA -- if you just separate out that group -- and, again, it's a small proportion of the total population but still fairly sizable. When you look at the total group, we had, I guess, well over 150, I think, in the reactogenicity subset and over 500 in the larger database of looking at unsolicited adverse events.

And when you compare that to the individuals that had no prior evidence of infection, it looks

basically the same. The point estimates actually look a little bit better, but obviously within the realm of statistical significance, we can't make much of that. But clearly these individuals did not fare worse from the vaccine. And I think we've not seen anything in terms of, as those individuals had tracked through the study, a particularly high attack rate or severe disease that would suggest to us that there's a problem in that group.

DR. ARNOLD MONTO: Okay. Dr. Kurilla, one part only.

DR. MICHAEL KURILLA: Thank you. If Pfizer were to receive an EUA and you lost all of the participants in the trial who were healthcare workers, would the remainder still allow you to have -- be adequately powered to carry on? That would be my first question. The other --

DR. ARNOLD MONTO: I said one part only.

DR. MICHAEL KURILLA: Well, I'm just going to put my hand up again, then, Arnold.

DR. ARNOLD MONTO: Then you go to the bottom of the queue. Okay. Please, that's an important question.

DR. KATHRIN JANSEN: So I would like to have Bill address this, and then we may also need help from Dr. Ken Currie (phonetic).

DR. WILLIAM GRUBER: Yeah. Thanks, Kathrin. So I think it's our current estimate, as best we can determine, that about maybe 20 percent or something north of that may fit into the health provider category. However, that still leaves, of course, 80 percent, given the highest attack rate, presuming that those placebo recipients remained in the trial for a while longer. We know that we would be in a good position, which is particularly sad given the high attack rate, that we could still track out and get a good measure both for safety and efficacy over the longer term.

I think the bigger challenge really relates to how quickly the CDC moves forward to the additional

tiers and how quickly those populations, again, get encompassed with an emergency use authorization and would be covered if we conform to the plan that we've outlined. But it's my sense -- and I'll ask Ken Currie, who's our head of stats just to comment on this. But it's my sense that, yes, even with 20 percent loss, we won't have that much difficulty. If we were sort of in the 50 to 60 percent efficacy category, that could potentially prove more challenging. I don't know. Dr. Currie.

DR. KEN CURRIE: Hi, this is Ken Currie. I lead the vaccines stats for Pfizer, and those answers are correct. The study is well positioned to continue to accrue more cases and to be able to answer some of these questions with more precision.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth? And please, let's keep it mainly to the discussion items.

DR. JAMES HILDRETH: Thank you, Dr. Monto. My question is for Pfizer, and it relates to the

recruitment of minorities into the study, which is relevant to number two. My understanding is that the minorities were recruited fairly late in the process. Do we have an adequate follow up to that group compared to the majority of the participants? The two-month median is what I'm referring to. Can someone address that for me? Thank you.

DR. KATHRIN JANSEN: I'd like Dr. Gruber to comment on the demographics.

DR. WILLIAM GRUBER: Thanks, Kathrin. Let me correct one, perhaps, incorrect assumption, which is that we actually from the very start were focused on targeting in recruitment from racial and ethnic minorities. What we decided to do, after we proved successful in terms of the overall success in getting to 30,000 and deciding how to move forward, we decided at that point, given that we'd had some success but we wanted to have more, we actually informed sites that to preferentially, beyond what they'd already done, in any new recruitment that they provided was really targeted

to minority communities. So it was a fact that we started from the very beginning, but then we further enriched at the end.

So I would say you can feel confident that minority communities were recruited throughout, perhaps with a bit more towards the end. But I'm convinced and I think the data supports that we had individuals from those communities followed for a long enough time, certainly to demonstrate efficacy, within the limits, of course, of some of the groups having a smaller number of total cases.

But it's not the right assumption that we didn't start from the very beginning. That was a key ingredient we advertised, both on our website and everywhere else that we could, about our intent to bring people of color into the trial.

DR. ARNOLD MONTO: Okay. Dr. Levy on the discussion items, please.

DR. OFER LEVY: Hi. My webcam isn't working. Can you hear me?

DR. ARNOLD MONTO: We can hear you. We don't need to see you.

DR. OFER LEVY: Okay. Fair enough. So my question is, in terms of gaps, this is a very big picture question. If we want to have a safe and effective vaccine deployed and make a huge dent in this pandemic, eventually what will be needed is high vaccine penetrance, right? 60, 70, 80 percent of the vulnerable population immunized. Would we realistically get there -- given the structure of the United States and the tendency of adults in the United States -- would we realistically get there without a pediatric vaccine?

And I realize there are all sorts of challenges and hurdles and counterarguments, but I'd be interested to hear from FDA and Pfizer if they've given long-term thought to the ultimate endgame here. Because if there were a safe and effective pediatric vaccine, obviously the infrastructure for vaccine delivery and penetration of vaccine is very favorable

in that regard. Thank you.

DR. ARNOLD MONTO: Let's keep the answer relatively short. That's a very big question. So Pfizer, pediatric plans?

DR. KATHRIN JANSEN: Bill, you want to take that?

DR. WILLIAM GRUBER: Sure. I'm happy to. We obviously recognize the importance of moving into the pediatric population. I touched base on this briefly in the main presentation.

We thought so strongly about this that, as you know, we obviously are trying to seek an indication in 16- to 17-year-olds, which we think is supported by what you've heard from us and the FDA. In addition to which, we already have 12- to 15-year-olds in the trial. Which not only informs the ability to move forward in that group where we're going to recruit 2,000 individuals, but actually also preliminary information which was submitted to the FDA from the first 100 individuals looks quite good compared to the

reactogenicity we're seeing in 18- to 25- and 18- to 55-year-olds.

So we're already embarking on that path, and then it's are intention, if all continues to go well -- and so far it has from a safety point of view -- to move down to 5- to 11-year-olds. Based on the nature of the data becoming available, the completion of where we are with the 12-to-15-year-olds, we anticipate that that will commence by April of 2021. And the idea would be to start there and then, as is typical for pediatric trials, once we have documented safety in that group move down.

It's our expectation, although I'm encouraged it might not necessarily be the case, that we may need to do dose ranging in the 5- to 11-year-olds. We thought that might happen in the 12 to 15, but they seem to tolerate the 30 microgram well. But once we move down to 5 to 11, we'll be very judicious just as we were in the 12 to 15, doing small sample of sentinels and then working our way down. And then,

ultimately, we propose to move down in younger age groups below five years of age. And again, we'd do that in a judicious fashion.

DR. ARNOLD MONTO: Dr. Krause?

DR. PHILIP KRAUSE: I just want to comment, if I can, on behalf of FDA, and that is Pediatric Research Equity Act actually requires there to be a plan for evaluating products in pediatric patients and in children. But, of course, there's also a requirement that you can't do research in children unless you have a prospect of benefit. And so, you can't do these studies initially in children, but I think moving quickly now the benefit of the vaccine has been established is a very reasonable thing to do. And that's something that we'll be working with the sponsor on. I'm wondering, while I have the floor, though, that I might drive things back towards the actual discussion items a little bit more.

DR. ARNOLD MONTO: Thank you.

DR. PHILIP KRAUSE: And in that regard, we

heard this morning from Dr. Goodman suggestions that we might look towards, instead of an unblinding when people become eligible for receipt of vaccine outside of a trial, a crossover design in which blinding is maintained. And of course, if one is to do something like that, that is the last opportunity in which one might be able to draw serum on people in the trial in order to determine whether they've seroconverted, which would then give a chance to look at the question raised earlier as to whether or not people have gotten infected while one still can compare a vaccine versus placebo.

So I don't know if anyone at Pfizer is prepared to opine on this, but do these seem like reasonable things for you to do? Instead of unblinding to do a crossover when people become eligible for a vaccine. But also to draw serum on these individuals before that happens to allow for this kind of additional look at the last moment before placebos, in essence, disappear and one then loses that opportunity

to compare also in the blood what happened to vaccinees versus placebo recipients?

DR. KATHRIN JANSEN: I can take that first question and comment. So we are fully planning to actually do the analysis of vaccine protection against asymptomatic infections very soon, as I noted, probably at the beginning or very early in 2021. So we can take under advisement to see if there is an opportunity or value based on our routine serum sample that we do in the participants anyway, if an additional blood draw would be of value. And then for the blinding question that you have, I would also give it back to Dr. Gruber to comment.

DR. WILLIAM GRUBER: Yes, thanks, Kathrin. Obviously, the considerations that were discussed by Dr. Goodman have been front and center for us in thinking about how we would move forward. We have looked at the issue of a potential crossover. And although there is some potential advantage, I think some things that are being advertised may be sort of a

false premise. Once, for instance, individuals know that they've received vaccine in both groups you sort have essentially equalized them in terms of their perception about whether they need to come in for illness visits or not. So that's a challenge.

Deferral in the circumstances is not an option for ACIP recommended groups, so that's a challenge in terms of, obviously, solving for our ethical obligations to vaccinate folks. There's also a logistic approach.

As I mentioned, when we're enrolling 22,000 individuals, somebody has to be first in line. We can't bring them all in on day one. So the idea was, okay, with the EUA authorization, we can kind of bring them in as that authorization and recommendation expands. On the other hand, if you're talking about a crossover where everybody is now going to have to come in for two additional visits, you're talking about --

DR. PHILIP KRAUSE: Well, of course, it'd be twice as many people. Of course, I think that what he

proposed was you'd only bring them in for crossover as they otherwise become eligible.

DR. WILLIAM GRUBER: Good point. Forty four thousand individuals would have to be brought in for two additional visits, and those individuals that are receiving vaccine would have to do this -- in essence, be reconsented, essentially agree to come back for two additional visits. Now, I heard Dr. Goodman appropriately saying that some of these people -- and we would hope that this would be the case if you chose that path -- would do this out of the goodness of their heart. But it does mean that they have to come back for an otherwise unintended -- or a visit back to a medical facility -- and the risks of exposure just from that sort of experience in and of itself.

So the notion of these -- what we're concerned about is that when we add this additional piece of work that these individuals have to not only agree to but provide informed consent for two additional visits for both groups, that creates -- potentially from their

perspective, maybe the risk-benefit equation isn't such a great idea for me, I'm going to just go ahead and wait my turn and get the vaccine.

So those are things -- you know, the logistics are something that are not trivial because we've got to bring in basically a lot of people to be vaccinated. And if we now add this to 88,000 visits, that's a challenge.

Obviously, we've enrolled 44,000 people and done 88,000 visits, but it took us a number of months to do that. So if the notion is trying to strike the right balance between getting people timely vaccination when their eligible, there are some advantages to be gained by just having to vaccinate the placebo recipients.

DR. PHILIP KRAUSE: Of course, one of the questions, and the way this is being put to the Committee, is that if you can't do this and you then lose the ability, for instance, to look more directly at the ratio of efficacy and already even in the

crossover design lose the ability to do in many people longer term follow up for safety -- and, of course, as it is the people who are at highest risk who are those who are also going to be suggested for earliest vaccination. And so you'll then lose the ability in continuing your trial to look at further impact on severe disease.

What are the ways in which the inability to get that information from continued follow up in the trial will be addressed? How can, well, the American people as well as the FDA and the CDC recommending bodies be sure that we have enough information to proceed with the vaccine, and understand exactly what the longer-term safety, durability, and efficacy against severe disease is?

DR. WILLIAM GRUBER: I mean, those are all reasonable questions and ones that we're wrestling with. But I think we've already sort of addressed the common reactogenicity. I don't think there's likelihood that you'll get much more precision related

to that. So if you set that aside, there is this period of time where we would expect we would continue to be able to collect information as the EUA rolls out and those individuals remain.

As I said, maybe 20 percent of the population would be vaccinated, and it will still take some time to do that. So I imagine we might be able to do that within one or two months. That's still -- even within that population, the time where we would be continuing to collect cases.

As far as safety is concerned, the same thing applies. You still would have a proportion of these individuals for looking for longer term events. As we move farther and farther out, the likelihood that you've got a vaccine related event, I think, becomes diminishingly small.

Part of the reason I think we were enamored with the idea of a median follow up of two months, is it's our perspective that if you're going to see something specifically related to vaccine, it's more

likely to happen in that time span. And you've already got a significant database to look at that.

And, of course, you don't lose the ability to look at efficacy over the long period of time. Let's suppose that all the placebo recipients ended up moving over to the trial relatively quickly. One of the key features is looking at durability of response, and you can look comparatively at the newly vaccinated -- and I think we heard this from Dr. Goodman this morning. You can look comparatively at the newly vaccinated compared to the previously vaccinated and determine whether or not you're beginning to see those individuals that -- previous vaccinees, if their curve basically starts sloping up and it becomes -- suggesting that you're losing protection.

DR. PHILIP KRAUSE: Although that analysis was based on a premise of blinded follow up.

DR. WILLIAM GRUBER: I'm sorry. I didn't hear that last comment.

DR. PHILIP KRAUSE: I think the analysis that

was put forward by Dr. Follmann of the NIH was based on a premise of blinded follow up, not of unblinded follow up.

DR. WILLIAM GRUBER: Yeah. But I'm talking about a circumstance where you would just be able to compare the attack rates in the respective groups based on the difference in terms of time as far as -- of course, that's predicated on what's happening with the pandemic.

It'd like nothing better than that the pandemic had gone away if we did that. But I think based on what I'm hearing from the experts, some of whom we heard from today, it's our expectation over the span of time we would plan to conduct this, that we would badly be in a position where we would likely be able to determine if in fact those attack rates for those people who were more remotely vaccinated went up.

DR. ARNOLD MONTO: Okay. Going to have two more questions, and then we are going to move into discussion of our voting question. So Dr. Chatterjee

and then Dr. Cohn.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. I'd like to address discussion item number two. Dr. Gruber, in your presentation, slide number CC58 I believe, you spoke about different studies that Pfizer might be conducting. But I did not see long-term care facility residents listed. They are obviously at high risk because of which they've been prioritized to receive the vaccine.

And the other one was inclusion of any concomitant use trials, particularly with influenza vaccines. At least in the Northern Hemisphere, this vaccine will be rolled out at a time when influenza vaccines are also being given. So does the sponsor have studies planned for those two populations or those two types?

DR. WILLIAM GRUBER: Kathrin, do you want me to go ahead and take it?

DR. KATHRIN JANSEN: Yeah. It was addressed to you, Bill.

DR. WILLIAM GRUBER: Okay. So let me address the second question first. I think it was on the slide. We do have a plan to potentially look at concomitant influenza vaccines, recognizing just the issue that you raised. It'll be great if you find that this vaccine manages to provide protections that's durable and no one requires an additional dose. And as we said, we're going to be looking very intently at the durability of protection.

But if that's not the case -- and the presumption is that over the course of the coming months we'll begin to get a clue about that -- then we would be considering looking at co-administration of influenza vaccine, assuming that that would be a timely period for annual vaccination if protection was not inferred.

I think the challenge that we encountered when we thought seriously about the long-term care facilities for a prospective trial, given the closed nature of that, getting the informed consent -- a lot

of logistic issues. And I think this isn't unique to us, I think it's common to a number of the other sponsors, except maybe the monoclonal antibody trial. That didn't prove to be fertile ground for us to be able to move forward to get a good answer.

I think we can take some comfort -- in fact, I'd say a great deal of comfort -- that when we look at the older populations that are engaged in our trial, that were showing efficacy, particularly, not only in people that are older but people older with comorbid conditions. Like obesity and Charlson Comorbidity conditions that I think would translate well into a high likelihood of protecting against individuals in long term care facilities. I might defer to Dr. Luis Jodar, who I know he and his team have thought about more long term follow up in terms of the nature of surveillance. I'm sure the CDC and others will be looking at those populations as well.

DR. LUIS JODAR: Thank you very much, Dr. Gruber. I'm Luis Jodar --

DR. ARNOLD MONTO: Very brief, please.

DR. LUIS JODAR: -- Chief Medical Officer for Vaccines. I do not have much to add, but I should say that we plan post-EUA studies in the next few weeks, the conduct of case-controlled test negative designs in which we can measure real world effectiveness, selecting specific populations. And we are thinking very much indeed to select long-term care facilities in those studies. Thank you.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Cohn and then we are going to start discussing the voting question. You're muted.

MR. MICHAEL KAWCZYNSKI: We still can't hear you, Amanda. Amanda, we can't hear you.

DR. AMANDA COHN: Okay. I apologize. Can you hear me now?

DR. ARNOLD MONTO: Yes.

DR. AMANDA COHN: I was wondering if you could tell us what the timelines may be for authorization or

approval in the other countries that you have enrolled trial participants in, which are Argentina, Brazil, Germany, South Africa, and Turkey? And what is the plan in terms of those countries, people continuing in this placebo randomized controlled design versus unblinding those participants as well at the same time as unblinding in the U.S.?

DR. KATHRIN JANSEN: Bill, please take that.

DR. WILLIAM GRUBER: Yeah. I think the brief answer is, again, our whole unblinding process is going to be done in cooperation with regulatory authorities, both here as well as elsewhere. I think we will take into account national recommendations, as well as local recommendations. So it is conceivable that we would be in a position to continue individuals in a placebo-controlled fashion in a blinded way in those countries.

But we have to be mindful of the fact of our ethical obligations regardless of geography. So it's going to involve a balance. If there's subtle differences, that's going to be probably easier for us

to make those sorts of adjustments than if, you know, take healthcare providers, chances are we might be providing this to healthcare providers across the board. But this is something we'll engage in based on our conversations with regulatory authorities both foreign and domestic.

DR. ARNOLD MONTO: Okay. Thank you. We are now going to close discussion of the discussion items and move onto discussion of the voting question. And could we bring up the voting question? So anybody who has their hands raised now should lower them because the next discussion is going to be about the voting question. And, Mike, can you bring that up?

I think we better see it before we start talking about it. Wording is very important. And I will even read it, even though you can all read it.

Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 vaccine outweigh its risks for use in individuals 16 years of age and older? Okay? Amanda,

is that -- are you asking to be recognized again, or is this the old one?

DR. AMANDA COHN: Yes, thank you. No, this is a new one. I got my hand up quickly this time.

DR. ARNOLD MONTO: Okay. Let's start with you.

DR. AMANDA COHN: I just wanted to comment that I do believe that the benefits outweigh the risks. I think that some language that I would prefer to be added to this language is, "based on the totality of scientific evidence available at this time."

And I do want to ask FDA to comment on potential other contraindications, besides history of anaphylaxis to a vaccine or warnings such as persons with a history of Bell's palsy or other things that they are including in the considerations.

DR. ARNOLD MONTO: FDA? Marion, Phil, Doran?

DR. DORAN FINK: Hi, so this voting question is what we would like the Committee to consider at this time, which is an all-inclusive authorization for ages

16 and above. If the Committee has concerns that the benefit-risk balance is not able to be assessed, or unfavorable such that it would preclude inclusion of a specific subgroup, then, clearly, we would want to hear about that and would consider those recommendations in contraindications or in the parameters of the population authorized for use.

DR. ARNOLD MONTO: The question is about groups within this 16 years of age and older, such as with some kind of underlying condition. Is that usually handled by FDA with information warnings, labels, or something like that?

DR. DORAN FINK: Well, it depends on what the reason for concern is. So if there is a clear risk that would make the benefit-risk balance so unfavorable that persons in that group should never be vaccinated, then that would be a contraindication. For lesser concerns than that, that might merit a warning or a precaution.

DR. ARNOLD MONTO: Right. Is that usually

something that is voted on by an advisory committee, those specifics?

DR. DORAN FINK: Typically, no. Those are handled through labeling.

DR. ARNOLD MONTO: All right. Okay. Let's go on to next Mr. Toubman.

MR. SHELDON TOUBMAN: Yes, thank you. So I'm going to ask the Committee or the other members listening this, I'm a consumer rep so maybe I'm a good indicator of how things are perceived by the public. But I have spent a lot of time reviewing the material trying to understand the data. And in light of concerns with the data expressed by my colleagues, many commentators, and in the literature, I do have a compromise proposal that's not (inaudible) the whole thing that was just suggested or even questioned. But rather it would be that EUA be limited to the groups that the CDC ACIP committee has already identified as priority.

And the data is limited, as we know. It's

limited in so many ways. The severe disease thing that I was talking about before, it's not compelling at all. I mean, FDA says all we can do is suggest protection from severe COVID-19 disease. We need to know that it does that. So that's one bit of data we need to get.

The safety issues are only two months of data. And I know it's been said many times that six weeks is usually the amount of time before we have a problem, but this is a completely untested technology with this vaccine in humans. And then the FDA says as far as a vaccine-enhanced disease over time, that's unknown. So there's a few of these missing pieces of data.

Given that we don't have good data on effectiveness on the thing that really matters, which is preventing severe disease and the safety issues, and that there's a question of duration of protection, which more time would give us, I think that what we absolutely need, as other people have said, phase 2/3 trial to continue. And we've also discussed at length how, if we grant EUA broadly, than it's going to really

present a problem.

I know that there's work arounds, and I understand -- it makes sense -- the blinded crossover people we're going to lose at that point, thereafter, the placebo benefit.

It's been suggested by Pfizer and others that we can go with the standard, that's wait until -- that people in the study will only be told and unblinded, or offered the crossover option, if it is authorized for their particular demographic to get the vaccine at that point. But what's been talked about is state and local standards. And as Dr. Lee pointed out, that is really problematic and variable. And I can tell you as an advocate on the state level, we can lobby successfully to get things change on the state level.

And maybe that's not so good. Maybe you need a clear standard of EUA. And as I pointed out earlier, a lot of the trial participants who are writing to us and complaining are viewing, "If EUA is granted, then that means I should get it." And we can disagree with

that.

But clearly, if EUA is officially granted initially only for the two high risks groups, which is identified by the CDC, which was healthcare workers and the nursing home residents to start, that will give us time -- give FDA time to review more thoroughly the data. It can be just a few weeks. And they could either come back to this Committee or on their own decide, okay, we now have enough to go forward and expand it to a larger population.

And the reason I'm suggesting this is obviously because the risk-benefit analysis changes, and you're talking about the hardest populations of persons (inaudible) given all the uncertainty. And the other piece of it is that we know there's just not enough to go around.

So even if you agree to what I'm saying, it makes no difference in terms of what's going to happen on the ground in terms of getting vaccine out, because it's only going to go, initially, to the healthcare

workers and nursing home residents anyway. But the reason why I think it's important, is it will allow the FDA the opportunity to get real data.

I did ask for the data for November 14 to today, just on severe disease. We know there were only 10 cases before November 14, and I couldn't get, when I asked, more recent data. I'm sure Pfizer today, right now, knows how many severe cases there were since November 14 in both groups. But that's the kind of data we really need to see, I think. And that's why I'm suggesting it.

DR. ARNOLD MONTO: Doran?

DR. DORAN FINK: Yeah. I'd like to make one point about this question of severe disease. I think it's important, and it was covered to some extent at the last VRBPAC meeting in October. And that's that we have able experience of examples of vaccines that protect just as well, if not better, against severe disease as they do against mild to moderate disease.

And so, protection against disease of any

severity is actually a pretty good predictor of protection against severe disease. We have a pretty strong result in terms of efficacy with this vaccine, based on the available data. And those data that we do have for severe disease are all point in the right direction and corroborate what history has shown us. I think that's important to --

DR. ARNOLD MONTO: Not only that, we'll get more data as we start using the vaccine more extensively, because with rare outcomes you have to start using the vaccine in order to see them under proper circumstances. I'd like to move on to -- Dr. Meissner's got the next question.

DR. CODY MEISSNER: Thank you. I would like to concur with what Dr. Fink just said that, if a vaccine prevents mild disease, I think we can assume it will prevent severe disease. So I understand that's the most important endpoint. But because the rarity of the severe disease, it may be difficult to reach that.

The other point I wanted to make about long

term safety. We know about the safety of this vaccine through 60 days. And it's pretty hard to think of a vaccine reaction that occurs after 60 days. And I looked through the vaccine injury table for conventional vaccines, and all of the injuries, except for one, were only up to six weeks, not even eight weeks. The one exception was a polio vaccine -- a live polio vaccine -- administered to an immunocompromised host. And this is obviously not a live vaccine.

So I think we cannot -- no one could say that there is no long term enhance immunity when the vaccinee experiences the vaccine. But to me, I think the safety is pretty well demonstrated. And balance that against over 2,000 deaths a day or 2,500 deaths a day, I'm comfortable. And if I could make one more point, Arnold. I'm sorry.

DR. ARNOLD MONTO: Go ahead.

DR. CODY MEISSNER: Yes. I am uncomfortable about the question as its written. I do not believe we have sufficient data for 16- and 17-year-olds. I would

prefer to say, "for use in individuals 18 years of age and older." 16- and 17-year-old children, as we saw, or adolescents do not get very sick, seldom get hospitalized, and I'll bet it's a very small number of deaths.

DR. ARNOLD MONTO: Phil, would you like to make a comment? And then I think we should talk about the 16- and 17-year-olds specifically. Phil?

DR. PHILIP KRAUSE: Yeah. I just wanted to make a specific comment about vaccine safety and duration of follow up. Because, I think, one of the important things to remember when we're rolling out a vaccine to many people, is that it's not just the side effects that the vaccine is causing that are important, but it may also be the vaccine side effects that are attributed to the vaccine, but which the vaccine didn't actually cause that are important.

That's one of the reasons why we typically to follow people in clinical trials for six months or more, and where that placebo-controlled follow up can

be very important in showing that whatever happened in the vaccine group also happened in the placebo group. Because that's our best way of knowing. And very often, it's the fact that we have that placebo-controlled follow up over time, that gives us the ability to say that the vaccine didn't cause something at a longer period of time after vaccination.

One could, in fact, argue that one could even get more placebo-controlled safety follow up over the shorter run, which then could expand the total safety database. This was proposed at a WHO meeting a few weeks ago where, as long as vaccine supplies are limited, there shouldn't be a prohibition against getting additional placebo-controlled follow up in people who don't have immediate eligibility for vaccine. And that then could expand the safety database to a much larger number than even what one is capable of doing in these trials.

But very often, these kinds of studies work very much to the benefit of the manufacturers because,

if one has this data, it actually allows one to say fairly definitively that a side effect that somebody thinks the vaccine is causing is not being caused by the vaccine.

And of course, this is something that is a big concern with rapid roll out of a vaccine -- this kind of thing caused big problems in 1975 and 1976. The swine flu vaccine where there were rapid cases of Guillain-Barre syndrome, where if there were more placebo-controlled data, one might have been able to address that at a different level. Although, that would have required very many patients.

But I'm just pointing out that it's not just the two months follow up in these phase 3 trials, which are important, but really placebo-controlled safety follow up can play a big role in helping us determine what the vaccine doesn't cause, which is often at least as important as our ability to determine what it does cause.

DR. CODY MEISSNER: Thank you, Dr. Krause.

DR. ARNOLD MONTO: Thank you. Does anybody in particular want to talk about the 16- and 17-year-old issue? I think that's an important one to get settled because it may be affecting how people would like to vote on this.

DR. OFER LEVY: Yeah. This is Ofer Levy. I want to speak to that issue. Is that okay?

DR. ARNOLD MONTO: Yeah. Please. And then Dr. Gans.

DR. OFER LEVY: Yeah. So a complicated topic, and it can be argued either way. Cody correctly pointed out that the incidence of severe COVID in 16/17 years of age is not high. On the other hand, we've already heard from Pfizer -- and this is quite typical -- that if they do eventually want to get a pediatric indication and the endgame could look -- we don't know. We don't have a crystal ball. But it's possible if you demonstrate safety in pediatrics that eventually you get this as a pediatric vaccine, and it's incorporated into the pediatric immunization schedule. That is a

very practical model because that's how most vaccines are distributed, around the world, through the infrastructure of vaccinology.

So in terms of achieving population penetration. So the loss, if we take away the 16- and 17-year-olds here, we lose what is the effort to climb down in age eventually, and we might lose one of our tools to eventually really conquer this pandemic. So I'm not so sanguine about removing that group.

DR. ARNOLD MONTO: Dr. Gans.

DR. CODY MEISSNER: Can I respond?

DR. ARNOLD MONTO: Dr. Meissner, go ahead.

DR. CODY MEISSNER: Thank you, Ofer. That's a very interesting point. So I think you're suggesting that if the 16- and 17-year-old subjects are not included then that will delay an approval, or authorization for young children? I don't think that's the case. You're muted.

DR. OFER LEVY: Okay. Hi. It will reduce the amount of information we have about the 16- and 17-

year-olds. It will slow down getting the vaccine to them. And if we don't have that information, it makes it that much harder to go down in age beyond that.

So I'm thinking about what the endgame here is for the entire world. As we know, these viruses don't know national borders. What's realistic is, you know, getting vaccines eventually that are safe and effective through the typical vaccine infrastructure in the world. Most vaccines are delivered in early life.

DR. CODY MEISSNER: But we don't know if the benefit outweighs the risk in that two-year age group, Ofer.

DR. ARNOLD MONTO: Let me interrupt. There were data in our briefing documents about studies going down to, I think, 12 years of age. If anything, there were larger numbers there than in some of the -- in the 16- and 17-year-olds. Anybody --

UNKNOWN SPEAKER: I'm sorry. Dr. Levy, why are you saying that a vaccine would have to have an emergency use authorization in 16-year-olds when they

probably -- where they're not going to be in the group that's going to get the vaccine. They're not going to be prioritized, but they'll continue to be studies in the trials. So I don't see how this interferes with the eventual total licensure for that age group.

DR. HAYLEY GANS: I think that's the important point here is, like, when they come into the phase. I think it's very important to study this group, and I think that we will have ongoing data on them. The question is does the risk-benefit actually outweigh it as this point?

And being a pediatrician -- and Ofer knows this very well -- I'm obviously a big proponent of any kind of studies that we can get into children, and we certainly need it for herd immunity. But they're not going to be first in line, and I do think we should allow the studies to continue that have been proposed and probably allow the people who have already been vaccinated to actually have sole safety data. So I would support not including them in this round.

DR. ARNOLD MONTO: Other pediatricians? Dr. Sawyer, did you have something you were -- Dr. Chatterjee?

DR. ARCHANA CHATTERJEE: Thank you. I've been trying to get in for a while to put in a word in edgewise.

DR. ARNOLD MONTO: Yeah. Well, it's hard.

DR. ARCHANA CHATTERJEE: I agree completely with what Dr. Gans and Dr. Meissner said. I have the same concern which is, among all the scientific data presented, I thought that the thinnest was for the 16- and 17-year-olds. Who, if they were eligible under this EUA, would not be granting permission themselves. Their parents are responsible, so they're not making the decisions themselves to get vaccinated or not.

The other group I had concerns with was the people who are 75 and older. But because of the very high risk for that group, I think it's reasonable to not put an upper limit on the age. But I too would vote for putting that age limit up to 18 and older.

DR. MARK SAWYER: This is Mark. I would like to just join that lineup of people advocating for that. I think the data is very thin, and it's inadequate to really say we have safety, given the low incidence of disease. I know the argument was they're going to going off to college, but I'm not sure how many are going to receive vaccine between now and then, given the staging of release of vaccine. So I would favor delay.

DR. ARNOLD MONTO: Dr. Rubin and then I'm going to ask FDA to respond. You're muted.

DR. ERIC RUBIN: I'm not a pediatrician, so I say this with some trepidation, but we're looking at lots of subgroups here. And I think we don't want to lose sight of we're very focused on safety, as we should be, because these are healthy people. But the efficacy is overwhelming for this vaccine. It's very, very strong.

And remember that we're going to be voting, if we vote for this, to approve this for Native Americans

-- and there were very few of those -- for nursing home residents, which weren't in the study at all. And we think that it's likely to work and it's likely to be safe because of what we know.

There are more 16- and 17-year-olds in the study than there are Native Americas, I suspect. And I'm not sure why we wouldn't want to provide clinicians the option of using those. Some of these kids are working in supermarkets and are going to be EMTs and essential workers. So I hate to take that tool away from clinicians.

DR. CODY MEISSNER: Can I comment, Arnold?

DR. ARNOLD MONTO: Yes, please, and then we want to hear from the FDA, what they would suggest at this point.

DR. CODY MEISSNER: Thank you very much for your comment, Dr. Rubin. I think the difference, for example, between American Indians and children is American Indians have a high rate of disease. 16- and 17-year-old children do not have high rates of disease.

So, it becomes a risk/benefit balance that worries me.

DR. PAUL OFFIT: As another pediatrician I'd like to chime in -- as the last pediatrician to chime in.

DR. ARNOLD MONTO: Here's what I would say. I think I support this statement actually as written. I think it's never an issue of when do you know everything, the question is when you know enough? We certainly know that this vaccine is highly effective for three months after dose one. We know that we have a lot of safety data and can say, as Cody pointed out, that at least we don't have a relatively uncommon serious side effect problem.

And in terms of safety, we're going to be doing follow up to make sure that issues like Bell's or anaphylaxis will be attended to. The fact of the matter is 16- and 17-year-olds can get this infection. And when they get it, we've seen, certainly, reports as well as children in our hospital who have had cardiac anomalies as 16- and 17-year-olds. And if you can

prevent this disease safely and effectively -- I mean, we have clear evidence of benefit. All we have on the other side is theoretical risk. So I frankly would support this as written. And I agree with Dr. Rubin.

DR. CODY MEISSNER: Can I respond to Paul? Arnold?

DR. ARNOLD MONTO: Yes, go ahead. Go ahead.

DR. CODY MEISSNER: Paul, the rates of MIS-C, at least as far as we know, and as was published in the *New England Journal* regarding New York State, the rates of MIS-C were two cases per 100,000 people under 20 years of age.

DR. PAUL OFFIT: Okay. But I'm not just saying MIS-C. There is also vasculitis that doesn't necessarily meet the operational criteria for MIS-C.

DR. CODY MEISSNER: Well, and that is certainly true. But I'm just saying that the rate of disease is so small, and we know so little in this age group. It's real. Believe me, we've had them, too. But I have a little more trouble justifying it in

children who are so unlikely to get the disease.

DR. ARNOLD MONTO: Can we hear someone from FDA, Doran, or Phil?

DR. CODY MEISSNER: Amanda's a pediatrician.

DR. ARNOLD MONTO: -- comment on this. I'd just like to hear what -- or Marion. Come on.

DR. MARION GRUBER: Okay. This is Marion. So I think I really don't want to throw in my own opinion on this. I hear the Committee's concern. I just think that, as Dr. Fink has discussed earlier on, our laws and regulations do also permit extrapolations to younger age groups. And we have been, I think, pretty forthcoming even in our briefing document that we would support an extrapolation.

One should also consider that 16- and 17-year-olds are out there. They may transmit disease. And the last comment that I wanted to make on this one is really, if the argument is made that 16- and 17-year-olds are really not the ones who are high risk group and would get in line to get this vaccine because

they're not within the recommended group, I think you can make the same argument for an 18- to 25-year-old. So to me, I don't find that that compelling.

I wonder, however, looking at it is 5:30 and, Arnold, we have a strategy -- I would like, provided that other Committee members do no longer want to weigh in -- I would like for the Committee to really vote on this question as is, to really hear -- because we have 23 members. And I would like to see the results and then we go to next, Arnold. That's my recommendation.

DR. ARNOLD MONTO: That is -- thank you very much. I was hoping for some direction because we are moving around in circles right now. So we are going to move to the vote. And again, the process is going to be this. We will vote on our computers. The votes will be announced, and then we will have an explanation of vote from those who wish to give an explanation of their vote. Okay? Kathleen, am I correct in the process?

MS. KATHLEEN HAYES: Yes, thank you, Dr.

Monto. So our members and temporary voting members that you'd be able to see on this slide, excluding the industry representative, will be voting in this meeting. And in regard to the voting process, Dr. Monto, as you mentioned, you'll read the question for the record. And then afterwards, all members and temporary voting members will cast their vote by selecting one of the voting options, which will include yes, no, or abstain.

You'll have two minutes to cast your vote after the question is read. And once all of the votes have been placed, we will broadcast the results and read the individual votes aloud for the record. So just please note that you have two minutes timeframe, and you can change your vote within that period of time. But after the vote has closed, all votes will be considered final. So are there any questions related to voting?

DR. CODY MEISSNER: Yes. Kathleen, can I ask a question? Cody Meissner.

DR. ARNOLD MONTO: Please.

DR. CODY MEISSNER: I want to vote for this vaccine. I just would like to remove the 16 to 17 -- I don't want to vote against the EUA just because I'm uncomfortable 16 -- can we modify the wording if this doesn't pass?

DR. ARNOLD MONTO: I think that's what Dr. Gruber was saying. Marion, would you confirm that?

DR. OVETA FULLER: I thought we just said we were not going to modify the wording so that we could get to a vote.

DR. MARION GRUBER: I would recommend voting on this question as is for now because we have not heard from all the Committee members.

MS. KATHLEEN HAYES: Thank you, Dr. Gruber.

UNKNOWN SPEAKER: Kathleen, can I ask one last question before we vote?

MS. KATHLEEN HAYES: If it's related to the voting process, sure.

UNKNOWN SPEAKER: Well, it is.

DR. ARNOLD MONTO: Only about the voting process, not the question. Okay. I think we are going to vote.

MS. KATHLEEN HAYES: Great. Let's pull up the voting question on the slide, and Dr. Monto you can read the question for the record.

DR. ARNOLD MONTO: Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 vaccine outweigh its risks for use in individuals 16 years of age and older? Your vote possibilities are yes or no, and if you want to abstain, you just don't vote. Is that it? Because I thought there was an abstention possibility.

MS. KATHLEEN HAYES: There's an abstain selection. The no vote just shows your name if you haven't made a selection.

DR. ARNOLD MONTO: Okay. So we have two minutes to vote.

MS. KATHLEEN HAYES: Yes. Go ahead and please cast your vote.

DR. CODY MEISSNER: How do we return the vote to you? Can you see what we've voted?

MS. KATHLEEN HAYES: Yes, once you select the radio button, I can see the vote. Mm-hmm. We have one minute remaining. 30 seconds. Okay. At this time, the two minutes is up, so if we could please close the vote and broadcast the results. And I will read the votes aloud for the record.

Dr. Moore voted yes. Dr. Cohn voted yes. Dr. Gans voted yes. Dr. Perlman voted yes. Dr. Kurilla voted no. Dr. Rubin voted yes. Dr. Levy voted yes. Dr. Pergam voted yes. Dr. Chatterjee voted no. Dr. Fuller voted no. Dr. Meissner abstained. Dr. Sawyer voted yes. Dr. Hildreth voted yes. Dr. Kim voted no. Dr. Monto voted yes. Dr. Tripp voted yes. Dr. Wharton voted yes. Dr. Gea-Banacloche voted yes. Dr. Offit voted yes. Dr. McInnes voted yes. Dr. Lee voted yes. Mr. Toubman voted yes.

And that concludes the vote, so we do have a favorable vote. And that concludes this portion of the

meeting, so I will now hand the meeting back over to Dr. Monto. Thank you, everybody.

DR. ARNOLD MONTO: Okay. Marion, do you have anything you want to add at this point?

MR. MICHAEL KAWCZYNSKI: We can't hear you, Marion.

DR. MARION GRUBER: I apologize. Double muted. I just wanted to thank the Committee for voting on this very complex topic. I wanted to thank the Committee for their discussion and their suggestions. We very much appreciate their input on this very important topic, and we will take what we've heard today into consideration when deciding on not only the EUA issuance here but also how to move on in the development and licensure of this product. Thank you so much.

DR. ARNOLD MONTO: And therefore, our work for the day is done. I wanted to thank the Committee. And I want especially to thank the FDA because they have been laboring long and hard, in doing the analysis,

dealing with some of the issues such as the recent anaphylaxis episodes. And I will therefore close the meeting, and I believe most of us are going to be revising some of these issues in about a week. So thank you very much. Goodnight and see you soon.

[WHEREUPON THE MEETING WAS ADJOURNED]