## ATTENDEES

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<tr>
<th>COMMITTEE MEMBERS</th>
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<tr>
<td>Arnold Monto, M.D.</td>
<td>University of Michigan</td>
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<td>Hayley Gans, M.D.</td>
<td>Stanford University Medical Center</td>
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<td>Archana Chatterjee, M.D., Ph.D.</td>
<td>Rosalind Franklin University</td>
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<td>CAPT Amanda Cohn, M.D.</td>
<td>Centers for Disease Control and Prevention</td>
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<td>Michael Kurilla, M.D., Ph.D.</td>
<td>National Institutes of Health</td>
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<td>Steven Pergam, M.D., M.P.H</td>
<td>Seattle Cancer Care Alliance</td>
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<td>H. Cody Meissner, M.D.</td>
<td>Tufts University School of Medicine</td>
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<td>Paul Offit, M.D.</td>
<td>The Children’s Hospital of Philadelphia</td>
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<td>Sheldon Toubman, J.D.</td>
<td>New Haven Legal Assistance Association</td>
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<td>Gregg Sylvester, M.D., M.P.H</td>
<td>Seqirus, Inc.</td>
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<th>TEMPORARY VOTING MEMBERS</th>
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<td>A. Oveta Fuller, Ph.D.</td>
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<td>James Hildreth, Sr., Ph.D., M.D.</td>
<td>Meharry Medical College</td>
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<td>David Kim, M.D., MA</td>
<td>U.S. Department of Health and Human Services</td>
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<td>James Neaton, Ph.D.</td>
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<td>Jeannette Lee, Ph.D.</td>
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<td>Stanley Perlman, M.D., Ph.D.</td>
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<td>Pamela McInnes, DDS, MSc.</td>
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<td>Harvard TH Chan School of Public Health</td>
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<td>Patrick Moore, M.D., M.P.H</td>
<td>University of Pittsburgh Cancer Institute</td>
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<td>Mark Sawyer, M.D., F.A.A.P</td>
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<td>Melinda Wharton, M.D. M.P.H.</td>
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<td>Steven Goodman, M.D., Ph.D.</td>
<td>Stanford University</td>
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**GUEST SPEAKERS**

- Tal Zaks, M.D., Ph.D. (Speaker) - ModernaTX, Inc.
- Jacqueline Miller, M.D., FAAP (Speaker) - ModernaTX, Inc.
- Melissa Moore, Ph.D. (Speaker) - ModernaTX, Inc.
- David Martin, M.D., M.P.H. (Speaker) - ModernaTX, Inc.
- Lindsey Baden, M.D. (Speaker) - Brigham and Women's Hospital/Dana-Farber Cancer Institute; Harvard Medical School
- Darin Edwards, Ph.D. (Sponsor Attendee) - ModernaTX, Inc.
- Nedim Altaras, Ph.D. (Sponsor Attendee) - ModernaTX, Inc.
- Charles Lee, M.D., J.D., CCHP-P, FACC (Sponsor Attendee) - American College of Correctional Physicians

**FDA PARTICIPANTS/SPEAKERS**

- Doran Fink, Ph.D. - Food and Drug Administration
- Marion Gruber, Ph.D. - Food and Drug Administration
- Philip Krause, M.D. - Food and Drug Administration
- Celia M. Witten, Ph.D. - Food and Drug Administration
- Peter W. Marks, M.D., Ph.D. - Food and Drug Administration
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<td>Rachel Zhang, M.D.</td>
<td>Food and Drug Administration</td>
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<td><strong>FDA ADMINISTRATIVE STAFF</strong></td>
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<td>Prabhakara Atreya, Ph.D.</td>
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<td>Kathleen Hayes, M.P.H</td>
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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. KAWCZYNISKI: All right. Good morning and welcome to the 163rd Meeting of Vaccines and Related Biological Products Advisory Committee meeting. I’m Mike Kawczynski, a project manager with FDA, and I will be today’s meeting facilitator. This is a live virtual public meeting that is being broadcast in its entirety through C-SPAN, YorkCast, Facebook Live, YouTube, Twitter, and a variety of other live streams.

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’ll 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, please manage your mute and activate your webcam.

Note to all members and participants, we are aware of the adverse weather conditions that we are
experiencing, and we've taken precautions. If we encounter any issues, we may have to take an unscheduled break. At this time, I'd like to now kick off the meeting and introduce Dr. Arnold Monto, the acting chair, who will now provide opening remarks. Dr. Monto, please go ahead, activate your camera, and take it away.

DR. MONTO: I'd like to add my good morning greetings to Mike's. Again, this is a meeting, the 163rd Meeting of the Vaccines and Related Biological Products Advisory Committee, affectionately called the VRBPAC.

We have one topic for today, a topic to discuss and vote on, the Emergency Use Authorization of the Moderna COVID-19 vaccine for the prevention of COVID-19 in individuals 18 years of age and older. First, I'd like to turn the floor over to Prabha Atreya, the designated financial -- federal officer, excuse me -- of the VRBPAC who will give us administrative announcements, the introduction of the
Committee, and Conflict of Interest statements.

Prabha.

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

MR. KAWCZYNSKI: Prabha, please unmute your personal phone.

DR. ATREYA: Okay. I'll start again. Good morning, everyone. This is Dr. Prabha Atreya, and it is my honor and great pleasure to serve as the Designated Federal Officer -- that is DFO -- for today’s 163rd Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research and the Committee, I would like to welcome everyone for today’s virtual meeting.

The topic for today's meeting is Emergency Use Authorization, EUA, of Moderna COVID-19 vaccine for the
prevention of COVID-19 in individuals 18 years of age and older. Today’s meeting and the topic were announced in the Federal Register Notice that was published on December 12, 2020.

I would like to introduce and acknowledge the excellent contributions of my team in preparing for the meeting. Ms. Kathleen Hayes is my backup and co-DFO providing support in all aspects of conducting this meeting. Other staff are Christina Vert, Jeannette Devine, and Monique Hill, who provided excellent administrative support. Thank you, team, for your support.

Please direct any press and media questions for today’s meeting to FDA’s Office of Media Affairs or fdaoma@fda.hhs.gov. The transcriptionist for today’s meeting is Ms. Allegra Chilstrom.

We will begin today’s meeting by taking a formal role call for the Committee members and the temporary members. When it is your turn, please turn on your video camera, unmute your phone, and then state
your first name and last name. 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. Arnold Monto? Mike,
can you project the roster slide?

**DR. MONTO:** I'm Arnold Monto. I'm a professor
of epidemiology in the School of Public Health at the
University of Michigan.

**DR. ATREYA:** Dr. Amanda Cohn. You have to
unmute your speakerphone.

**DR. COHN:** Thank you. Good morning. I'm Dr.
Amanda Cohn. I'm Chief Medical Officer at the National
Center for Immunization and Respiratory Diseases at the
CDC.

**DR. ATREYA:** Thanks. Dr. Chatterjee. Archana
Chatterjee.

**DR. CHATTERJEE:** Good morning. I'm Dr.
Archana Chatterjee, Dean of the Chicago Medical School
and Vice President for Medical Affairs at Rosalind
Franklin University. I'm a pediatric infectious
diseases specialist by training and background, and my interest is in the field of vaccines.

DR. ATREYA: Great. Dr. Cody Meissner.

DR. MEISSNER: Good morning. My name is Cody Meissner. I am a professor of pediatrics at Tufts University School of Medicine and Tufts Children's Hospital. Thank you.

DR. ATREYA: Great. Dr. Sylvester. Gregg Sylvester.

DR. SYLVESTER: Good morning. My name is Gregg Sylvester, and I'm the non-voting industry representative. I am the Chief Medical Officer at Seqirus, and I'm a pediatrician and general preventative medicine doc by training. Thank you very much for having me.

DR. ATREYA: Okay. Thank you. Dr. Hayley Gans. Dr. Gans?

MR. KAWCZYNISKI: She's relogging back in, so let's go. We'll come back to her. Go ahead.
DR. ATREYA: Okay. We can move on Dr. Michael Kurilla.

DR. GANS: Hi. This is Hayley Gans. Can you hear me?

DR. ATREYA: Yes.


DR. GANS: Hi. This is Dr. Hayley Gans, a professor of pediatrics and pediatric infectious disease from Stanford University. Good morning.

DR. ATREYA: Thank you. Dr. Kurilla, now.

DR. KURILLA: Good morning. Mike Kurilla. I am a pathologist by training. I am the director of the Division of Clinical Innovation within the National Center for Advancing Translational Sciences within NIH. Prior to that, I was at the National Institute of Allergy and Infectious Disease, working on vaccine drug and diagnostic development. Prior to that a stint in industry doing drug development, and then past experience in academia doing clinical microbiology.
DR. ATREYA: Thank you. Dr. Paul Offit.

DR. OFFIT: Yeah. Hi. Good morning. I'm Paul Offit. I am a professor of pediatrics at Children's Hospital of Philadelphia and at the Perelman School of Medicine at the University of Pennsylvania.

Thank you.

DR. ATREYA: Great. Mr. Sheldon Toubman.

MR. TOUBMAN: Good morning. My name is Sheldon Toubman. I'm an attorney at New Haven Legal Assistance in New Haven, Connecticut. I represent low income individuals mostly in the area of access to healthcare. But I'm here today in my personal capacity as a consumer representative.

DR. ATREYA: Okay. Thank you. Dr. Steven Pergam.

DR. PERGAM: Hi. I'm Steve Pergam. I'm an associate professor at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington. And I'm an infectious disease clinician by trade.
DR. ATREYA: Thank you. Next slide please.
Mike? Mike, can you present the next slide please.
Thank you. Dr. Fuller.

DR. FULLER: Good morning. I'm Oveta Fuller.
I'm an associate professor at the University of Michigan in the medical school in microbiology and immunology, and a member of the STEM Initiative at the African Studies Center at the International Institute, and I'm a virologist by training.

DR. ATREYA: Okay. Dr. David Kim.

DR. KIM: Good morning. David Kim. I'm the division director at the Division of Vaccines in the Office of Infectious Disease and HIV/AIDS Policy in the Office of Assistant Secretary for Health, HHS. Thanks for having me.

DR. ATREYA: Thank you. Dr. Eric Rubin.

DR. RUBIN: Good morning. I'm Eric Rubin. Welcome from a very snowy Boston. I'm a microbiologist at the Harvard TH Chan School of Public Health, an infectious disease physician at the Brigham and Women's
Hospital, and editor-in-chief of the *New England Journal of Medicine*.

**DR. ATREYA:** Excellent. Thank you. Dr. James Hildreth.

**DR. HILDRETH:** Good morning. I'm James Hildreth. I'm the President and Chief Executive Officer of Meharry Medical College. I'm also a professor of internal medicine and a viral immunologist by training. Thank you.

**DR. ATREYA:** Thank you. Next, Dr. Jeannette Lee.

**DR. LEE:** Good morning. I'm Jeannette Lee. I'm a professor of biostatistics at the University of Arkansas for medical sciences and happy to be here. Thank you.

**DR. ATREYA:** Thank you. Dr. Mark Sawyer.

**DR. 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 San Diego. I am a pediatric infectious disease specialist.
DR. ATREYA: Thank you. Dr. Melinda Wharton.

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

DR. ATREYA: Thank you. Dr. James Neaton.

DR. NEATON: Good morning. This is Jim Neaton. I'm a professor of biostatistics in the School of Public Health at the University of Minnesota.

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

DR. McINNES: Good morning. My name is Pamela McInnes. I'm retired as deputy director for the National Center for Advancing Translational Sciences, one of the NIH institutes.

DR. ATREYA: Thank you. Dr. Patrick Moore.

DR. MOORE: Good morning. I'm Patrick Moore -- Pat Moore -- and I'm a professor at the University of
Pittsburgh Cancer Institute and also in the Department of Microbiology and Molecular Genetics.

DR. ATREYA: Thank you. Dr. Robert Schooley.

DR. SCHOOLEY: Good morning. I'm Robert Schooley, professor of medicine in the Division of Infectious Diseases at the University of California, San Diego.

DR. ATREYA: Thank you. Dr. Stanley Perlman.

DR. PERLMAN: Good morning. I'm Stanley Perlman at the University of Iowa. I'm in pediatric infectious diseases and microbiology, and I have a long-standing interest in coronaviruses and immunology.

DR. ATREYA: Great. Thank you. Now, I will do introductions for the FDA staff. I would like to introduce Dr. Marion Gruber, Director, Office of Vaccines, who will say a few welcome remarks. Dr. Gruber, please turn on your camera and unmute your phone so everyone can see and hear you. Thank you, Dr. Gruber.
DR. GRUBER: Yeah, Good morning. My name is Marion Gruber. I'm Director in the Office of Vaccines Research and Review in the Center for Biologics Evaluation Research at the FDA.

I would like to welcome the Committee members, Moderna, and the public to today's meeting. I want to thank the VRBPAC members who are convening again today. We're looking forward to your thoughts and comments regarding the scientific evidence that will be presented by Moderna and the FDA. We also look forward to your perspectives on whether the benefits of Moderna's COVID-19 vaccine outweighs its risks to support authorization of the vaccine and then EUA for prevention of COVID-19 in individuals 18 years of age and older. I look forward to the discussions and thank you.

DR. ATREYA: Thank you, Dr. Gruber. I would also like to acknowledge the presence of Dr. Celia Witten, Deputy Director of CBER, and Dr. Philip Krause, Deputy Director, Office of Vaccines at this meeting who
may chime in as needed later on in the meeting. Also Dr. Peter Marks, our Center Director, will join us shortly after I complete the reading of the Conflict of Interest statement to make his remarks.

Now, I proceed with the reading the Conflict of Interest statement. Thank you.

The Food and Drug Administration is convening virtually today on December 17, 2020, the 163rd meeting of the Vaccines and Related Biological Products Advisory Committee, also known as VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Arnold Monto is serving as the acting voting chair for today's meeting.

Today, on December 17, 2020, the Committee is meeting in open session to discuss the Emergency Use Authorization, EUA, of the Moderna COVID-19 vaccine for the prevention of COVID-19 in individuals 18 years and older.

The topic is determined to be of particular matter involving specific parties. With the exception
of industry representative members, all standing and
temporary voting members of the VRBPAC are appointed
Special Government Employees, SGEs, or Regular
Government Employees, RGEs, 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 today, all members,
RGE and SGE consultants of this Committee have been
screened for potential financial conflicts 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, CRADAS, teaching, speaking, writing, patents, and royalties, and their primary employment. These may include interests that are either current or under negotiation.

FDA has determined that all members of this Advisory Committee, both regular and temporary members, 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, who have financial interest, when it is determined that the Agency’s need for the special government employee’s services outweighs the potential for the conflict of interest. They also may be authorized when the conflict of interest of the regular government employee is not so substantial and deemed not likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda, and all financial interests reported by the Committee members and consultants, there has been one conflict of interest
waiver issued under 18 U.S. Code 208 in connection with this meeting.

We have the following consultants serving as temporary voting members at this meeting today: Dr. Oveta Fuller, James Hildreth, David Kim, Jeanette Lee, Pamela McInnes, Patrick Moore, James Neaton, Stanley Perlman, Eric Rubin, Mark Sawyer, Dr. Robert Schooley, and Melinda Wharton. Among these consultants, Dr. James Hildreth, a Special Government Employee, has been issued a waiver for his participation today to participate at the meeting. The waiver was posted on the FDA website for public disclosure.

Dr. Gregg Sylvester, of Seqirus Incorporation, will serve as alternate industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve only as nonvoting members of the Committee. Industry representatives on this Committee is not screened for financial conflicts of interests and do not have voting privileges. Also industry representatives act on
behalf of all the 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, therefore, are screened and cleared
prior to their participation in the meeting. They are
voting members of the Committee.

Today’s meeting has one external speaker, Dr.
Steven Goodman, who will serve as the guest speaker.
He has been asked to disclose any financial interest he
may have related to the product before the Committee.
Disclosure of conflict of interests of guest speakers
follow applicable federal laws, regulations, and FDA
guidance.

FDA encourages all meeting participants,
including open public hearing speakers, to advise the
Committee of any financial relationships that they may
have with any affected firms, its products, and, if
known, its direct competitors. We would like to remind
standing and temporary members that if discussions involve any of products and firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from such discussions 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 invite our Center Director, Dr. Peter Marks, to make a few remarks welcoming the Committee. Dr. Marks, please, could you turn your camera on and the speakers unmute your speakerphone, and the floor is yours now. Thank you. Go ahead, Dr. Marks.

DR. MARKS: Well, good morning. Thanks, thanks, Prabha. Good morning. I'd like to take a moment, first of all, to welcome you all and also to provide a brief overview of advisories committees and the role they play in assuring transparency in FDA's decision-making processes.
FDA uses advisory committees to obtain advice from experts who work outside of the government. It does so while working towards an open and transparent government by presenting information under consideration in a public forum and encouraging patients, healthcare providers, and other interested people to share their views during the open public hearing or by submitting comments to the docket.

A key part of FDA's mission is to evaluate new therapies and determine which are safe and effective for their intended uses. This complex job often involves many areas of expertise, and sometimes FDA turns to outside experts for counsel such as for the COVID-19 vaccine under consideration today.

Advisory committees weigh the available evidence and provide scientific and medical advice to the FDA on the safety, effectiveness, and appropriate use of products that the Agency regulates. FDA advisory committees are just that: advisory in nature.

It's important to note that the advice that the FDA
receives from the committee does not represent the
position of the FDA, rather the FDA weighs the advice
that it receives when taking actions on medical
products. FDA ultimately makes the final decisions on
all matters that come before the committee.

Also, to set expectations for today's meeting,
we've organized the agenda topics slightly differently
than last week's meeting to allow the Committee members
to have sufficient time for a robust discussion of the
questions before them. We invite the public and the
Committee to review the presentations and recording of
the December 10th meeting for more information on
COVID-19 epidemiology, vaccine safety and effectiveness
monitoring, and operational distribution plans as those
will not be covered in depth today as they were at the
last meeting.

As we begin today's proceedings, I want to
take the opportunity to thank you all, including all
the Advisory Committee members, for the insights that
they'll provide and also thank the FDA staff, the
sponsor, and those presenting at the open public
hearing today for participating. Your contributions
are very important in helping us at well-reasoned,
science-based decisions. Thanks very much, and we look
forward to the meeting today.

DR. ATREYA: Okay. Great. Thank you, Dr. Marks. Now, I would like to hand over the meeting back
to our chair, Dr. Arnold Monto. Dr. Monto, take it
away.

DR. MONTO: Thank you very much, Prabha.

First, we're going to hear from Dr. Doran Fink, Deputy
Director of the Division of Vaccines and Related
Products Applications at FDA, who will give us a
presentation on Emergency Use Authorization. Dr. Fink.

FDA PRESENTATION ON EMERGENCY USE
AUTHORIZATION
DR. FINK: Hi. Good morning. If the AV staff could please make me a presenter, then I will begin my presentation.

In the meantime, I'll introduce myself. I'm Doran Fink. I'm the deputy director for Clinical Review in the Division of Vaccines and Related Products Applications, Office of Vaccines, Research, and Review, Center for Biologics Evaluation and Research at FDA.

The COVID-19 pandemic continues to worsen in the U.S. and worldwide. As of the week ending December 15th, there have been a total of 16 million cases and greater than 300 thousand deaths in the U.S. to date and 1.5 million cases and greater than 17 thousand deaths just in the past week.

On December 11th, just last week, FDA issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine. This vaccine is authorized for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. The EUA was issued after the December 10th VRBPAC.
meeting to discuss the vaccine, data informing its
benefits and risks, and plans for its further
evaluation.

On November 30th, Moderna Therapeutics
submitted an EUA request for the Moderna COVID-19
vaccine, otherwise known as mRNA-1273. This, like the
Pfizer vaccine, is an mRNA/lipid nanoparticle vaccine,
and it is administered as a two-dose regimen, 28 days
apart. The requested use for this EUA is for active
immunization to prevent COVID-19 caused by SARS-CoV-2
in individuals 18 years of age and older. The
information submitted with the request include safety
and efficacy data from a large, randomized, blinded,
placebo-controlled Phase 3 trial.

FDA has been conducting a comprehensive review
of the Moderna COVID-19 vaccine EUA submission received
on November 30th. As with the Pfizer request, our
review has been comprehensive and conducted over a
short period of time. We have verified clinical data
integrity and integrity of Moderna’s analyses and
conducted our own independent analyses from datasets provided in the submission.

We have conducted ongoing review of manufacturing, non-clinical and clinical assay information, including information that has come in in the last few days. We have reviewed and worked on revisions of prescribing information on fact sheets necessary to inform vaccine recipients and healthcare providers. We have had multiple information requests to Moderna to address our questions and need for clarifications, and, of course, we have prepared for today’s VRBPAC meeting.

This will sound like a bit of broken record, but I say it again because it’s important. Today’s VRBPAC meeting continues FDA’s commitment to an expedited review process that is transparent, scientifically sound, and data driven.

As a reminder from material presented last week, the legal authority for Emergency Use Authorization was established in Section 564 of the
Federal Food, Drug, and Cosmetic Act. It 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.

HHS Secretary Azar issued a declaration on March 27th justifying Emergency Use Authorization of drugs and biological products to address the COVID-19 pandemic, which is a necessary prerequisite for issuance of an EUA.

Here again are the criteria for FDA Issuance of an EUA. The agent referred to in the EUA declaration must cause a serious or life-threatening disease or condition. Again, we know this to be true for COVID-19. The medical product must be effective or must be believed to be effective to prevent, diagnose, or treat the serious or life-threatening disease or condition caused by the agent. The known and potential benefits of the product, it outweighs the known and potential risks of the product. And also there must
not be any adequate, approved, and available
alternative to the product for diagnosing, preventing,
or treating the disease or condition.

As I explained last week, there is only one
FDA-approved product for COVID-19, which is remdesivir,
approved for treatment and not for prevention.

As I mentioned at the beginning of my talk,
the Pfizer-BioNTech COVID-19 vaccine is now available
unapproved, and its quantity is not sufficient for mass
vaccination needed to address the pandemic in the U.S.
Therefore, the fourth criterion is still met.

FDA explained in guidance, and in a VRBPAC
meeting on October 22nd, our expectations for data and
other information to support issuance of an Emergency
Use Authorization for a COVID-19 vaccine. This
information includes data to demonstrate manufacturing
quality and consistency. And similar to the case with
the Pfizer vaccine last week, FDA has reviewed the
manufacturing information provided by Moderna and found it to be adequate to support issuance of an EUA.

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 vaccine safety and effectiveness, including an ongoing clinical trial, active and passive safety monitoring during use under EUA, and observational studies.

Last week, I had a number of slides outlining more details of these expectations. In the interest of time, I'm going to skip those today.

If an EUA were to be issued for the Moderna COVID-19 vaccine, it would specify the conditions of use for which benefit-risk has been determined to be favorable based on review of the available data. These conditions include the populations to be included in the EUA, conditions for vaccine distribution and
administration, and requirements for safety monitoring and reporting of adverse events.

Vaccine made available under EUA will also be accompanied by information for vaccine recipients and healthcare providers by way of prescribing information and fact sheets. These will describe that the vaccine remains unapproved and under investigation, under IND. They will describe the known and potential benefits and risks of the vaccine and will also discuss available alternatives and the option to refuse vaccination.

As I explained last week, an EUA that is issued may be revised or revoked for a number of reasons: if circumstances justifying the EUA no longer exist; if criteria for issuance are no longer met; or if other circumstances arise that warrant changes necessary to protect public health or safety, for example, based on new information concerning vaccine safety or effectiveness, vaccine manufacturing or quality, or COVID-19 epidemiology or pathogenesis.
I want to pause here to address the issue of anaphylactic reactions or serious allergic reactions following vaccinations. While today's discussion is about the Moderna vaccine, at last week's meeting we reported on anaphylactic reactions that occurred in the United Kingdom in two recipients of the Pfizer vaccine, which is also an mRNA and lipid nanoparticle vaccine and, therefore, relevant to today's discussion. Both of these vaccine recipients had a medical history of serious allergic reactions though not, as far as we know, to any of the vaccine components.

Yesterday, as has been reported in the press, two healthcare workers in Alaska experienced allergic reactions minutes after receiving the Pfizer vaccine: one of them an anaphylactic reaction resulting in hospitalization. All of these individuals were treated with appropriate medical interventions and, thankfully, all are recovered or recovering.

We anticipate that there may be additional reports, which we will rapidly investigate. We learned
of these cases through established safety surveillance systems that worked exactly as designed. And FDA is coordinating with CDC to further investigate the cases in the U.S. and to communicate our findings in a timely manner with vaccine providers and recipients.

FDA and CDC are also in close contact with public health and regulatory authorities in the United Kingdom as they continue their investigations. While the totality of data at this time continue to support vaccinations under the Pfizer EUA, without new restrictions, these cases underscore the need to remain vigilant during the early phase of the vaccination campaign.

To this end, FDA is working with Pfizer to further revise a fact sheet and prescribing information for their vaccine, to draw attention to CDC guidelines for post-vaccination monitoring, and management of immediate allergic reactions. This revision will be in addition to the information already included in the contraindications and warnings, including that
facilities where vaccines are being administered should ensure that medical treatment for managing serious allergic reactions is immediately available. We will do the same for the Moderna vaccine should it be authorized for use under EUA.

Here is the agenda for today's VRBPAC. As Dr. Marks mentioned, we have a lighter schedule than last week to allow for more robust discussion. You will see that some of the presentations from last week are absent because the information has not materially changed. We will have a repeat of Steven Goodman's talk on considerations for placebo-controlled trial design if an unlicensed vaccine becomes available. I will explain the reasons why on my next slide.

Following Dr. Goodman's talk, we will hear a sponsor presentation of the data for the Moderna COVID-19 vaccine. You will then have an open public hearing followed by a lunch break. And finally, an FDA presentation of our EUA review, discussion items, and questions for the committee to discuss and vote.
We have just one question today for discussion without a vote. This question is similar to one we asked last week, but we've rephrased it in a way that we hope will focus the discussion.

The reason we are coming back to this question is because it's important. The case-driven vaccine trial conducted in the midst of a pandemic that very quickly demonstrates clear evidence of efficacy, at least in the short term, and allow the vaccine to be made available under EUA. On one hand, this has a very positive effect of helping to address the pandemic. On the other hand, wide-spread vaccine availability can interfere with conducting the trial to completion.

To be clear, FDA has never insisted that placebo recipients enrolled in ongoing trials who want the vaccine, be made to wait beyond when the vaccine would otherwise be available to them under the conditions of EUA, prioritization recommendations, and available supply. Rather, we have been asking those responsible for conducting COVID-19 vaccine trials to
think carefully and creatively about how to continue trials after a vaccine becomes available under an EUA, to preserve whatever societal value can be preserved, and to ensure that sufficient data are ultimately approved to support vaccine licensure.

This includes encouraging study participants who are willing to remain in blinded follow up, for the same altruistic reasons that prompted their enrollment in the first place, to do so. Later today, you will hear about Moderna’s plans for their trial.

The question that we would like you to discuss is in considering Moderna’s plans for unblinding and crossover of placebo recipients: Please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in either ongoing clinical trials with the Moderna COVID-19 vaccine or other studies, such as additional clinical trials or observational studies with that vaccine.
Following this discussion, which again will not have any vote, we will have a single question for VRBPAC discussion and vote. And that question is, “Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older? Thank you very much.

DR. MONTO: Thank you, Dr. Fink. We have a full 20 minutes for discussion here. I think we should restrict our discussion to the EUA process and its characteristics.

Since we're going to be hearing from Dr. Goodman about some of the other issues, we probably should restrict questions or discussion about that until after he presents. So raise your hands please if you would like to make a comment. And Dr. Meissner.

DR. MEISSNER: Thank you, Dr. Monto. First, I would like to express my gratitude to Dr. Fink, Dr. Marks, Dr. Gruber, and their colleagues at the FDA for the extraordinary amount of work that has been put into...
this issue over the last few weeks and months. I think that all the citizens of the United States should recognize the enormous effort that has been put into this. So thank you.

My question is as follows, and it's somewhat similar to the question that I asked last week. It's important that we move a vaccine from an EUA to a BLA because there are a number of advantages to have a vaccine licensed and recommended by the CDC. Is there any way you can anticipate how soon that might happen? And does the availability of a second messenger RNA -- a vaccine with a similar mechanism of action -- will that facilitate the decision in any way for the FDA?

**DR. FINK:** Thank you for that question. As I believe I responded last week, we are actively working with the vaccine manufacturers, both Pfizer and Moderna, to arrive at a data package that would support vaccine licensure. This data package would include some additional follow up from clinical trials as well as data accrued from use under the EUA, as well as some
additional manufacturing information for vaccine that
is intended to be produced following licensure. So it
is our goal to arrive at a licensure application as
quickly as possible as the data allow.

And, in terms of your other question,
certainly new vaccines that are similar in platform,
although not exactly the same, will be considered
relevant to each other and will inform our assessment
of those respective vaccines.

DR. MEISSNER: Thank you.

DR. MONTO: Dr. Kurilla.

DR. KURILLA: Thank you. Doran, I want to
make sure that I understood what you said. You seemed
to imply that the issuance of a second EUA was partly
dependent on the fact that there was inadequate supply
of the initial EUA for mass vaccination. Is that a
criteria that would potentially impact the decision on
future EUA for other vaccines?

DR. FINK: So thanks for the opportunity to
clarify that question. So actually, the supply of
Pfizer vaccine is secondary at this time for considering issuance of an EUA for a different vaccine. And that's because the Pfizer vaccine is not approved. So consideration of available alternatives requires that those alternatives both be approved and adequate. So the fact that the Pfizer vaccine is not approved means that there is currently no approved available and adequate preventive vaccine for COVID-19.

**DR. KURILLA:** Thank you.

**DR. MONTO:** Dr. Rubin.

**DR. RUBIN:** Thanks, Dr. Fink, for that very clear presentation. I'm curious what FDA will do with the discussion item on Dr. Goodman's proposal. Is it likely to end up as an FDA requirement or a strong recommendation to proceed to BLA for the manufacturers?

**DR. FINK:** As I explained before, we are working actively with the vaccine manufacturers on accruing data that would be necessary to support a biologics license application. And this includes discussions around the contours of their ongoing
clinical trials going forward. We are hoping that the committee discussion will help to inform those discussions with the manufacturers.

**DR. MONTO:** Dr. Perlman.

**DR. PERLMAN:** Yes, so I just have a question about one of the last things you were talking about. So the anaphylactic reactions have clearly been a big deal in the press, and I and probably others get lots of calls about what it means. I think the FDA recommendations talk about allergies to components of the vaccine, yet the components of the vaccine actually are not obviously to me allergenic. Do you have any sense for how the FDA's going to finally make recommendations?

The U.K. has different recommendations than the FDA came out with. So do you know this is going to play out, and do you know what the components are in the vaccine that could be inducing this?

**DR. FINK:** So, at this point, we and CDC are continuing to investigate these cases and consider
data. At this point, we don't have enough information to make definitive recommendations one way or another. And, as we continue to investigate and evaluate the data, we will consider whether additional recommendations need to be made.

DR. MONTO: Dr. Pergam.

DR. PERGAM: Thanks, Dr. Fink, for that clarity, again, and for a short presentation because I know we have a lot to discuss today.

I had a question. You brought up the issues of a couple of separate question in addition to the main EUA question that we're going to be reviewing, related to what other studies need to be done, et cetera. I want to be clear. Is this for both vaccines, since we did not get to review those and give those recommendations to the Pfizer-BioNTech vaccine? Those discussions for additional studies or additional work that needs to be done, are those going to relevant for both vaccine candidates?
DR. FINK: Well, they certainly will be relevant for both vaccines. We'd like this discussion today to focus specifically on Moderna's plans. But clearly, the ideas discussed will be relevant to both vaccines.

DR. PERGAM: Thank you.

DR. MONTO: Dr. Moore.

DR. MOORE: For the long-term safety, meaning beyond years, even decades-long safety, for this vaccine and the other vaccines requires obtaining a centralized resource that allows us to know who is vaccinated and who is not. Is that being planned to be collected for -- outside of the randomized control trial? Is there a plan to collect that information to securely store it so that you can do linkage analysis with the cancer registries or autoimmune registries?

DR. FINK: So, as discussed last week, the U.S. government is planning a number of studies leveraging healthcare claims databases to evaluate vaccine safety over the longer term with use under an
EUA. I'm not the expert on those studies, and so I would have to defer comment on the details to those who are spearheading them.

DR. MONTO: Dr. Fuller.

DR. FULLER: Thank you, Dr. Monto, and thank you, Dr. Fink, for your explanations. The question, which may be addressed later, but I'll ask you, how will the FDA or CDC or other state health agencies monitor the potential adverse events that happen, like the allergies that you mentioned in Alaska? If it were a continuing clinical study, those would be picked up by the researchers. But, in this case, how will that be done? Could you please share a little bit more?

DR. FINK: Sure. And this was also explained last week in one of the presentations by CDC that we don't have today, but I'll refer you and refer the public back to the recording of that presentation. We have robust safety surveillance and reporting systems that have been in place for a long time including VAERS, the Vaccine Adverse Event
Reporting System. Additionally, vaccine recipients under the EUA will be asked to partake in a program called V-safe, which is an electronic safety reporting system that the government is using to track vaccine safety with use under the EUA.

DR. FULLER: All right. Thank you.

DR. MONTO: Dr. Neaton.

DR. NEATON: Thanks, Dr. Fink. My question is actually similar to Dr. Pergam's. Have you considered aligning some of the future protocols for these two vaccines in a manner, and also the current protocols with the purpose of being able to combine the data from each of those studies?

DR. FINK: Well, yeah. Combining or pulling data involve complicated statistical considerations. But what we have done -- and we discussed this at our October 22nd VRBPAC meeting and also in our guidance released in June of this year -- is we have recommended standardized case definitions that will help to evaluate efficacy results from trials of different
vaccines, not necessarily for comparing one vaccine to another, although that is one possibility. We hope that this standardized approach, which as we explained in October, is not a requirement for the primary endpoint but a recommendation that we've made for inclusion in all of the Phase 3 trials.

We hope that this will facilitate the type of broad and robust data analysis that you might be thinking of.

DR. NEATON: Yeah.

DR. MONTO: Dr. Gans.

DR. GANS: Thank you very much. Thank you, Dr. Fink. I had one question about -- I realized today we're entertaining the Moderna vaccine. We've now entertained the Pfizer one previously. And I'm wondering in the context of other vaccines that are coming to market -- all of which are going to have different adverse events as well as different populations in which they should be used.
I'm wondering in the context of equity in terms of how we role these out -- some are coming obviously into use before others. I just worry a little bit about how we should think about that in the context of the broader field of different vaccines that are coming that have different profiles. Have you had any thoughts on that, or how the FDA and CDC are thinking about those other vaccine models in the context of this?

DR. FINK: Sure. So, to be clear, FDA's responsibility is to evaluate data concerning the benefits and risks of the vaccine in the context of the Emergency Use Authorization request. And once FDA issues an Emergency Use Authorization, then the responsibility falls to CDC and the Advisory Committee on Immunization Practices to set prioritization recommendations and other recommendations for use of the vaccine, considering its benefits and risks in the populations included in the Emergency Use Authorization.
DR. GANS: Thank you.

DR. MONTO: Dr. Chatterjee.

DR. CHATTERJEE: Good morning. I have a question with regard to the BLA applications that may be coming from the manufacturers. In the past from my experience anyway, usually a BLA application comes in after the clinical trials have been completed. For these vaccines, is there a plan -- I couldn't quite understand from your explanation, Dr. Fink -- whether there will be interim data analyses, and we won't actually have to wait until the trials are completed before the BLA applications will be entertained by the FDA?

DR. FINK: Yeah, thank you for that question and the opportunity to provide clarification. Though it's actually not unusual for a clinical trial to be ongoing for longer term safety and/or effectiveness follow up when a biologics licensed application is submitted. At this point, we do have interim data for two COVID-19 vaccines. One of which we have authorized
for emergency use, another of which we are considering today. At this point, the data would not be considered quite sufficient to support a biologics license application. But as I mentioned before, we are working with both manufacturers to accrue the data that would be needed with the goal of getting these vaccines licensed as soon as the data allow.

We heard from Pfizer last week that they are anticipating potentially submitting a biologics license application sometime in the spring of next year. And that plan is certainly within the realm of what we would consider possible.

**DR. CHATTERJEE:** Thank you very much.

**DR. MONTO:** Dr. McInnes.

**DR. McINNES:** Good morning, Dr. Fink. I have a question regarding the status of inspection of facilities. And the reason I think this becomes important for us to have some sense of where you all are in this, was this availability of information on the news about unexpected volumes left in syringes.
So, while that may very well just be due to residual volume in syringe and needle of a particular type, verses what might be seen in another situation, it does bring up the question of the confidence in the manufacturing site, the manufacturer, the fill, the consistency. And while I appreciate that a full picture of that is not required under EUA, I would like to have some sense of the sort of confidence of the FDA in that particular state of data.

**DR. FINK:** So I can repeat that we have reviewed extensive manufacturing information for this EUA request and do feel confident that we have enough information to justify issuing an EUA for this vaccine, should everyone agree that the benefits outweigh the risks based on the clinical data. I can't speak in more detail about the facilities' inspections. I'd invite other FDA colleagues who might be on the line to chime in if they have something additional to say.

The other thing I'll mention about the volume issue for the Pfizer vaccine, is that if you look at
the instructions, they are to add 1.8 mls of diluent to
0.45 mls of vaccine that's already in the multidose
vial. It gets you to a total of 2.25 mls. And so,
with a dose volume of 0.3 mls, it is actually not at
all unexpected that there would be more than five doses
in those vaccines -- or in those vials.

**DR. MONTO:** Any further FDA comments? Okay.

Let's -- for the final question, Mr. Toubman.

**MR. TOUBMAN:** Thank you for the excellent
presentation, Dr. Fink. I have a question about the
FDA's review of the efficacy data. Your slide
indicated a November 30th mission for EUA. The
briefing documents indicate that Moderna submitted
another set of documents on 12/7 and that included --
so, instead of a close date of 11/7, it's a close date
of 11/21. And in the briefing document, you indicated
FDA has reviewed some -- and verified -- some of that
more recent data, but not all. You could just briefly
explain what that actually means?
And there's been reports in the press about how the FDA's process is more rigorous than the British review process, for example. But just briefly explain what that really means. And second, to confirm that you have been able to verify the efficacy data in the second set according to primary endpoint as well as the important secondary endpoint of any severe disease.

DR. FINK: Yes, we'll hear more about that in our FDA presentation this afternoon. But I can verify, I can confirm, that FDA has examined, verified the integrity of, and confirmed the efficacy analyses from the later timepoint, from the November 21st timepoint, both for the primary efficacy analysis and for the secondary analysis of severe cases.

What we have not done, due to time constraints, is more in-depth probing of the data to do our own independent analyses on some questions that we look at that are maybe not so central but of interest.

So all this to say that we have verified and confirmed Moderna's analyses for both the interim and
final efficacy analyses, those that we consider to be most critical to inform the benefit-risk assessment. We have not done quite as comprehensive a dive into those data as we did for the interim analysis, but we don't think that this should hinder in any way our confidence in the data to support an assessment of benefit and risk.

DR. MONTO: Thank you. Okay. We're moving on now to the presentation from Dr. Steven Goodman. And he'll be telling us about the considerations for placebo-controlled trial design if an unlicensed vaccine becomes available. Dr. Goodman is Associate Dean of Clinical and Translational Research at Stanford University School of Medicine. Dr Goodman.

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

DR. GOODMAN: Morning. Can you hear me fine?

DR. MONTO: Yes.
DR. GOODMAN: Okay. Terrific. So thank you so much for inviting me and, in fact, particularly for inviting me back again. I think the reason for that was presaged by the questions and talk just given, which is that the issues we'll be considering here are not just relevant for this vaccine, but for many trials currently ongoing and those in the future. So this arguably has potentially more long-lasting effect than even the EUA today.

I don't want to scare you with this title, which looks exactly the same as last week. I'm, in fact, not going to be giving exactly the same talk. I'll be picking up from where we left off last week and taking a bit of a deeper dive to give you more material for your discussion.

And this is the outline, I'll very briefly remind you where we left off after last week, then go into the Moderna consent and proposal. Then we'll take a bit of a deeper dive into the deferred vaccination design which we talked about last week. Then I'll
discuss the evidential and ethical effects of both partial and complete unblinding of the placebo group, which are both under consideration right now. Then I'll have a final single slide on the evolution of design, which is a perspective I hope you will consider in your comments. And I already heard a suggestion of this from Dr. Gans in her last question.

So let's go just to very briefly summarize where we were after last week. We had an ethical summary where we talked about the issue of ethical dilemmas as being a choice between two "right" actions or just justified in different ways which is certainly what we're going to be facing today even more starkly; the importance of trust in the whole vaccine development process and prioritization, which enables us to do these clinical trials and could be withdrawn at any time; talk a bit about the issue of context where the ethical calculus depends not only what we know and what we don't but the availability of vaccine; and we talked ethically relevant benefit in the sense
that whether the placebo group was taking on such a risk relative to the vaccinated group that they were owed something just by nature of that benefit. And the argument was that they were not, even though there was some very, very small deficit. But, of course, you don't know that when you sign up for the trial. We only know that in retrospect.

In terms of the epistemic or evidential summary. I'm just going to use the word evidential more today than epistemic, even though I'm really talking about the same thing. Which is that all designs can generate valid evidence albeit with different efficiency and degrees of certainty, that's randomized control trials, quasi-experimental and observational designs and, in particular, knowledge of mechanism and biology, which guides a lot of the interpretation of the empirical design.

And finally, that RCTs are best to assess some vaccine properties but not necessarily all. So they're
very good for some things, but we have to partition
between the things it's good for and not.

And finally, the idea that there shouldn't be
any bright lines drawn either on the ethics or the
epistemology fronts, and we shouldn't be declaring
anything particularly unethical. What we're really
saying when we use that word is we believe that one
principle outweighs another. And the word "unethical"
sort of disenfranchises people on the other side and
demonized them, and it doesn't lead to good
discussions, as well as strict adherence to
randomization when that's not necessary.

So let's go into the Moderna consent and
proposal. The consent is at the beginning exactly what
you expect. It mentions voluntariness. It is
particularly important that the participants may or may
not benefit from participating in the study, but it is
designed to help others in the future; that they can
leave at any time, this won't affect their future care.
Then we get into some of the questions which state in very plain language what the participants should expect, and it says what will happen at the end of the study. Basically, you'll just be discharged from the study by your doctor. Will you be informed if new information becomes available? Yes. And certainly, as with last week, the EUA is part of that.

But this is the most important clause here at the bottom. "Can you continue getting the study vaccine after the study?" And this is what was told in the consent: "If you choose to withdraw from the study or are taken out of the study, you will not continue receiving the study vaccine. Also, if the study is terminated early, or when the study is ended, the Sponsor will not continue providing the study vaccine."

Now that will be highly relevant to the actual proposal, which we will contrast here.

So, first of all, an observation was made that there's going to be a large number of folks who are eligible for early vaccine administration. This, in
particular, 25 percent of the enrollees are healthcare workers. But here's the proposal: they will proactively reconsent participants who received placebo and then offer them the vaccination. And then they will be observed unblinded for the rest of the entire two years, and adverse events will be captured. But basically, they are proposing to simply unblind and immunize the placebo group.

This is importantly different from last week's proposal, which was to wait until they were eligible for receipt otherwise. And then, if they asked, they would then be unblinded and immunized and that all participants would be encouraged to stay in this randomized trial as long as possible and that everybody would be immunized at the end of six months.

So this is different in multiple ways. First, that it's done immediately. Second of all, that they be unblinded. That actually is common to both. But that we don't wait for eligibility outside the trial. So this is a very, very, very important difference and
something that will have, as I will argue, consequences not just for this trial but for other trials of other vaccines.

So this is exactly the same as what we talked about before. What is owed to placebo participants. And this really is, what is the obligation? And that's something that can be asked of the investigators or the company because it's owed to them. And the simple answer is what's in the consent? That's what owed to the placebo participants, that the conditions upon which they enrolled. And of course, all the adherence to the Belmont ethical principles.

They certainly would want to expect that they wouldn't be denied the vaccine if it became available to them, which could be done through an exclusion to EUA, but I don't think that is actively being considered. And potentially, reciprocity, which is really a form of gratitude and not obligation, could be operationalized through higher priority for vaccine within their priority group when they become eligible.
But there's not an ethical obligation of investigators to unblind on demand. It is if there's a medical reason, but not for others. And not immediate vaccination with trial before their turn is called outside the trial. And that's actually reflected in the consent. If this was an ethical obligation to immediately vaccinate, once there was interim results showing efficacy or even with an EUA, this would have been in the consent, and it was.

So now let's take a little bit of a deeper dive into the deferred vaccination design. We showed this slide last week, there really are two alternative designs at this point that might be considered for this or future trials. One is this deferred immunization, which is a blinded crossover design, and second is active control designs.

I'm not going to focus on those, but I will talk about the implications of the guidance on this placebo group for the future of active control design. That's very important. And of course, everything comes
with active and passive observational studies of almost
every aspect of the vac- -- not just safety of the
vaccine properties. So both approaches are going to
require some give on the evidentiary and ethical side.

So this is a picture you saw last week. This
is the deferred vaccination arm. On the top, you see
the arm that gets immediate vaccine, that's in blue.
That narrows, and the narrowing reflects a slow waning
of the vaccine efficacy. Of course, we don't know if
or when that happens, but this is just a schematic to
show you how they can be still compared if we crossover
blindly.

On the bottom, you see the placebo arm and the
point at which there's early efficacy established which
is roughly where we are today, is still in Period 1.
And then the proposal is that at some point, if
somebody is going to become eligible for vaccine, that,
if they are in the vaccine arm, that they get a placebo
injection. And that, if they're in the vaccine arm --
I'm sorry, the placebo arm, they get a placebo -- I'll
get this straight. If they're in the placebo arm, they will get a vaccine injection.

So everybody ultimately gets immunized, but they still don't know whether they were in the immediate vaccination arm or in the deferred vaccination arm. And this preservation of blinding, even with the immunization of everybody in the trial, allows a number of things that I'll talk about in a minute, and I mentioned last week.

So this is another way to represent what's going on, and here we're measuring efficacy, not as the thickness of a bar, but in terms of attack rate. And the attack rate is on the vertical axis. And what you see is the attack rate you'd expect under placebo in the early days -- and on the bottom is just time -- would be high. Here it's just nominally indexed at one.

That would be the attack rate, and the red line are the placebo group, and at the bottom would be the attack rate in the vaccine group. In fact, in
practice this turned out to be much, much lower --
roughly 95 percent lower -- than the red line.

And then we watched them over time, and the
vaccinated arm, if vaccine efficacy starts to wane --
if and when -- what you would see is a slow rise in the
attack rate in the vaccinated group, and that the blue
line's starting to ramp up.

But, of course, there are other things going
on in the world that affect the attack rate, including
problems in the community, community restriction
measures. So there's a lot of things going on in
calendar time that need to be controlled for, which is
why we can't just observe what happens over time. We
won't know, if the attack rate starts to go in the
vaccine arm, exactly what it's due to.

So this is where the deferred vaccination can
still help us recover that information. And you see
that vaccination occur with a big drop, at the point of
deferred vaccination from the red line, down to a new
blue line. And we watched this attack rate for a while.

And if there's a difference between the attack rate in the early vaccinated group versus the late, that is a sign that there's waning of efficacy. And, of course, this can occur at every point. They could be at the same level for a while, and then the early vaccinees start to -- their efficacy starts to wane and their attack rate goes up over time. It doesn't have to be right at the point of crossover.

So this is what it looks like, and this is how you can recover this really critical information about how long this immunity lasts, which is going to be a major question. And we will also see that there are a few other things we can do with this design.

So I want to make the point that the crossover can occur whenever an individual participant becomes eligible for an available vaccine outside the trial. So it's not occurring for everybody at the same time, which those schematics suggested. It's occurring for
each individual potentially at a different time. I'll talk more about that issue of design.

There's also some unexpected benefits: one is that blinded crossover allows for more safety assessment via self-controlled design. And you'll see here on the bottom that for the placebo arm, we're looking very, very carefully at adverse event incidents in the post-placebo period. That serves as a control for the AE seen in the vaccine arm, which I sort of erased up here. I'm only looking at the placebo arm, and you'll see why.

And then when they cross over blindly -- of course, they don't know that they're crossing over -- we can then watch very closely adverse event incidents post-vaccine. And we can compare the AEs after this vaccination to before in a particularly powerful way, which is with control within each individual.

This is not just comparing overall incidence rate, which is like what's occurring in that first period. It's a self-controlled design, which controls
for confounding in a particularly powerful way. So this is a nice benefit of this design because they're being watched carefully in that first period. So this is very solid AE information.

We could ask people if they had a recent stroke or heart attack or whatever, before entering the trial, but they -- for certain AEs -- might not remember it very well. And certain ones might prevent somebody from enrolling. So this guarantees that there's absolutely no bias about who's included.

There's another bonus, which is that as vaccine efficacy wanes, if it does wane, the differed vaccination allowed the booster trial sort of right on top of the trial infrastructure. And, in that sense, it's an added benefit if we find that a second booster -- that is a third shot -- is need. And this can be piggy backed right on top of the deferred vaccination structure. So this, again, is a very nice add-on if needed.
Now, last week, that company was asked about whether they were amenable to doing this. They pointed to the logistics of maintaining the blind. They said it was very difficult and maybe not worth it. I will say that there are additional logistics, and it will be up to you to explore the yield and to give FDA advice on whether this is a determinant in whether it's worth going, or worth instituting.

So there's mandatory crossover serology, plus a dummy shot, and there's another dummy shot for both arms. Because neither one can know which arm they were in. There are possibly more blood draws, and these have to be synchronized between the two groups. They should be done and kept on the same schedule so serology is comparable.

And finally, there is reconsent, but this is necessary for any major design change, including unblinding and administration of vaccine. So this is not necessarily an additional logistical barrier. But what's really critical is that, in theory, no one knows
their assignment. And all the parameters, all the reasons we do the RCT, apply here in preventing bias and ascertainment of a whole bunch of AEs, efficacy endpoints, and even crowd participation as I will mention.

So this is complicated, but I'm actually not going to go through it in detail. I'm just going to point out two things. This is a list of all the things we still want to learn about the vaccine that is not really captured very well at this interim point, which includes duration of immunity after two months. This actually under certain circumstances can be enhanced by the deferred vaccination design even over continued placebo control, even though I think that's off the table.

And the other thing that's enhanced, which is really critical, and this is the link for the future is correlates of immunity, because we are now doubling the vaccinated arm. We're doing so in this randomized way. And we can enhance the finding of surrogate markers of
protection, which will be absolutely critical for active control designs in the future. I mentioned a variety of things here that are partly preserved; that is we'll be able to get some information but not necessarily definitive information.

Now finally, effects of complete or partial placebo unblinding, both on the evidential and ethical scale. In terms of partial unblinding, which would be done if we gave the vaccine to those at the point they became eligible. So we would never completely unblind the group until maybe some timepoint in the future as Pfizer recommended, but not as Moderna's proposing.

So it's important to mention the same fraction of vaccine recipients would also be unblinded. Because when they asked to be unblinded, or when they become eligible, they don't know what group they're in. So people in either group will be unblinded, and we'd lose them both at least to the randomization.

The remaining cohort, therefore, will probably be at lower risk, and the higher risk ones will be the
ones we will either potentially -- they will request unblinding or we will offer the unblinding because they become eligible.

Once a vaccinated person realizes they've been vaccinated, they will probably engage in higher-risk behavior, which will, for at least the one to two months after the unblinding, will make them a more difficult comparison group to the placebo group.

And finally -- not finally -- patient-reported outcomes for the unblinded group can be biased in terms of how people interpret various symptoms. They'll be an impaired ability to evaluate waning vaccine efficacy in the first six to eight weeks after crossover. After eight weeks, everybody knows they've been vaccinated, but, before this time, that vaccine efficacy is uncertain.

And it has unpredictable effects on trial retention, particularly safety assessment visits post-crossover. Because once you do the unblinding, there's a sense that, well, the experiment is over. You know,
you're coming back, you’re giving information, but we
don't have the same sort of bonding to the trial in the
sense that adherence to the dictates are actually
critical for validity.

If we were going to completely unblind the
placebo group, then we lose a lot from the evidential
side. There's no comparison group to compare rates of
infection or safety. So the duration of protection and
long-term hazards will be much more poorly assessable:
very unpredictable effect on retention, again, in the
sense that the trial is over. Quality of evidence for
licensure will be only marginally different than that
for the EUA because of what we've giving up.

Actually, it weakens the scientific value of
the trial that is pledged to the participants on
enrollment. This can easily be done if there are good
reasons, but shouldn't be done if there are good
alternative, particularly ones that give them the
vaccine anyway.
Finally, this may make placebo-controlled trials more difficult for other vaccines. We have a very strong interest in developing good information for those other vaccines because there will be a precedent, that as soon as something has been shown to be effective and it's available, that it's unethical to ask people to wait any more time to be immunized in any way. And this is a precedent you may not want to set.

I have a couple slides here on what the value of having more vaccines is. I actually think this committee knows it very, very well. They could have different immunization properties. We might find that they're better in combination, and they might have different safety profiles and acceptance. It might have different distribution and uptakes. But I'm not going to go through this, but you have these slides available.

So the last few slides, I just want to talk about the ethical impact on the unblinding, which is the trust in the whole trial system. Immediate
unblinding of vaccination could become a precedent and
a de facto expectation for others, perhaps undermining
either ongoing or new placebo-controlled trials. A
sense could take hold that even temporary withholding
of vaccination within a trial is “unethical” because it
was done in preceding trials.

I would suggest that the images of -- we have
to remember that what happens -- what we're doing here
if we do unblind, is we're disturbing the priority set.
That is we're going to be vaccinating young, low-risk
trial participants. And this will get out in the
community very different than the pictures we saw after
the authorization last week where it was healthcare
workers and others. So the images of young, low-risk
trial participants being knowingly vaccinated before
much higher-risk community members could adversely
affect trust in the fairness of the vaccine testing
system and the allocation system.

We'll then start looking very closely the
trial recruitment and enrollment procedures on all
trials, to see how we are choosing people who are in the trials who then will jump the queue. And that is a scrutiny we may or may not want to have done so aggressively, that the enrollment in the trial is, in a sense, a privileged position with regard to trial vaccine administration.

And it may be dangerous to have different ethical-evidential tradeoffs made in each trial, by each company -- and there are a lot more coming as you know -- thereby also bypassing societal priority setting for vaccine access. These priorities are generally regarded as fair, partly because the processes that created them is perceived as fair. If these are overridden in individual trials, there could be very unpredictable effects on perceptions by groups underrepresented in the trials and by the public.

If these trade-offs are trial and company specific, then there'll be a rush by some current and prospective participants to game the system in their favor -- because everybody'll be looking for the trial
that does better by them -- thereby undermining an
ethos that we are all in this together, and that we
need to act collectively for the greater good.

So this trial-by-trial resetting of the
ethical prioritization system, I think, is something
that we have to think about from a large -- with a wide
lens. And here's the widest lens, which is the
evolution of designs that we're going to be
experiencing as EUAs are issued. And we're, right now,
at this very early point where there was no EUAs or
vaccine is unavailable to some folks.

And that's the only context in which we can do
these placebo-controlled trials. And we're getting the
benefit of those right now, but we're very rapidly --
in fact today and last week -- moving into this new era
where there's some EUA's available, some vaccines
available.

And then we might find that the deferred
vaccination RCT's planned from the inception, not this
conversion, will become the standard. That is we
believe that we can reasonably ask people to put off vaccination for a few months, but, in the consent, it will say, after a few months you will be vaccinated.

I believe we're going to very rapidly move into that, and that asking for these trials to be in that category would be a great precedent to allow that transition so future studies can be designed with that.

Finally, once we get the BLAs issued -- the approvals -- we're probably going to have to move into an era -- and I don't know exactly when this will be, but probably sooner rather than later -- where the only RCTs we're able to do in populations that have the vaccines available are active control RCTs. And, for these, we really need good surrogate endpoints. We really need good correlates of immunity, and that's what we're getting -- we have the opportunity to get right now. And if we undermine that, it's going to weaken the interpretability of the later active control RCTs.
So I'd like to strongly encourage you to look, take the long view, look at this as a vaccine development ecosystem. And then, if we can keep the same standards for all of the trials, particularly the priority setting for vaccine administration -- and, as I mentioned, none of the current international priority setting agreements include participation in a trial as a priority, unless of course you fall in traditional high-risk groups.

So, if we're consistent across all trials, I think, they'll both be more comparable, we will enhance trust in the system, and we'll be consistent across the board. If we start making it company-by-company, trial-by-trial exceptions, I think, we're going to run into, rather quickly, problems with trust and retention.

So, with that, I will thank you for listening, yet again. And I want to, in particular, thank the participants in the trial so far who've enabled us to have this conversation today, whose contribution was
and will continue to be a tremendous gift to all of us.

Thank you very much.

DR. MONTO: Thank you very much, Dr. Goodman.

You went over a bit, but this was a very important presentation for our further thinking. I just want to reiterate what you have said, and that is that the crossover is not really just one design, it's a design which will vary by when a crossover is done. Am I correct in that?

DR. GOODMAN: Uh, yes. And one thing I'll also add is that it doesn't necessarily have to be for individuals. It could be that the stage -- that the crossover is staged by priority group. That if it’s preplanned every two weeks or every month, the next priority group will come in. But, yes, it does depend on when it's done, and you want to maintain it as long as you can, as long as it's practical.

DR. MONTO: And this could be part of future consent forms. So you don't have the logistic challenge now of reconsenting individuals.
DR. GOODMAN: Yes, absolutely. This could be prespecified, and I think as the design of the trial, that the trial from inception is designed this way. And it seems inevitable, honestly. If we're talking about converting these placebo-control trials into this, it's hard to imagine doing a complete placebo trial going forward. So I do think that is what we will evolve to, but that's something you can discuss.

DR. MONTO: Okay. We have about ten minutes now for discussion, but we're going to circle back and rediscuss all of this after we hear the sponsor presentations. Okay. Dr. Chatterjee, please. And I think some people have unmuted their phones.

DR. CHATTERJEE: Dr. Goodman, thank you for your presentation. I wanted to ask this question last week actually, which is, is it not going to be difficult to maintain the blind in any of these crossover trial designs that you're talking about. Because of the difference in the adverse events, the vaccines are clearly much more reactogenic than the
placebo. But at least the recipient, and presumably the people conducting the trial, would become aware of, or could guess, which product they received.

DR. GOODMAN: Absolutely. I do think for a certain subset of folks, they will be able to guess more often. But remember there's a fair overlapping in symptoms. That is, even things like chills, which you would think would be vaccine specific, are occurring in the placebo group as well. So it is true that that symptom and others occur more often, absolutely, in the vaccine group. But the occurrence of any of these symptoms won't necessarily unblind.

And still it won't be as complete an unblinding. It's really all relative, obviously, as that you tell people, this is what you got. People may well suspect that. I don't think they necessarily act in ways that assume that they were vaccinated. For example, if that happened, you would imagine that people in the current trials or in future trials, when they got those reactions would go out with very high-
risk behavior. That's really what we're trying to avoid, but absolutely.

All I can say is it will occur more with the unblinding than it will with a continued blind. And we're trying to preserve as much as we can for valid inferences. But you're absolutely right, this is not -- and it's true in also in therapeutic trials as well. So it's a relative issue. It's not that this completely unblinded with the blinding -- I'm sorry -- that blinding is perfect, but it's much better.

And also there's this other sense of sort of staying within the experimental framework and not leaving the trial and making it impossible. We haven't even talked about, you know, further follow up, whatever, and retention for all the other endpoints.

So you're right about that, but I still think it's preferential from both an evidential point of view than basically just telling everybody which arm they were in.

DR. CHATTERJEE: Thank you.
DR. MONTO: Dr. Meissner.

DR. MEISSNER: Dr. Goodman, I would like to thank you again for another very thoughtful and clear presentation on this really difficult issue.

I'd like to make a comment and a question. As a former chair of the Vaccine Injury Compensation Program, it's important to have as careful an understanding as we can reasonably acquire from longer-term follow up of vaccinees. I think the Vaccine Injury Compensation Program has had an enormously favorable impact on the uptake of vaccines in the United States, and has resulted in the highest uptake of vaccines in history.

I would certainly encourage the blinded crossover design that you have proposed, because that may give us some opportunity to evaluate long-term complications between a vaccinated group and an unvaccinated group. So I would just like to support that.
And then the second question I have, and it may not be answerable, but has Pfizer made any decision as to how they're going to follow subjects based on your first presentation? Thank you. Over.

DR. GOODMAN: Actually, that will have to be your last question about what Pfizer will do, and obviously today is not about that. But you could ask the same question about what the consequences will be in the decisions for Moderna as well. I don't know. That's going to be a question for the FDA. I don't know what the nature of their conversations with either of these companies about the requirements in the BLA.

I think that's where this will play out, not necessarily in the EUA but in the subsequent request for the kind of information they would like for the BLA. And I don't know what is happening as a consequence of after last week's meeting, just as I probably will not know after this week's meeting. But that is something for you to ask the FDA, and ask the
FDA representatives what they're working for or what
they think they can ask.

DR. MONTO: Dr. Kurilla.

DR. KURILLA: Thank you. Dr. Goodman, this
has to be one of the most insightful, ethical
discussions I've been privileged to listen to, so thank
you for that.

The question I have concerned the ongoing
trials. If we were to do a blinded crossover, I'm
wondering how two populations would be handled. The
first is people who actually develop COVID, what do we
do with them? Are they done? Do we just -- they just
fall out or? And the other population, because of the
unreliability of serology in this regard, that unless
you catch it in the very post-acute phase, you may not
necessarily be able to recognize someone, there's going
to be an increasing percentage within both arms from
asymptomatic infection, and they may be contributing to
immunity and that's going to complicate. I'm just
wondering how you think going forward that can be handled appropriately with those populations?

DR. GOODMAN: Yeah, fantastic question. So there was a line in my slide of what we could learn that said, for the ability to prevent infection -- which is really catching the asymptomatic -- and infectiousness, other designs may be needed. So this won't necessarily capture that well unless you did very frequent serology. And even then, as you say, the serology's not perfect.

So this means we can capture a little bit of that, particularly if we increase the number of serologies. We almost certainly can't do that if they're not retained in a semi-randomized study. And that's all I will say.

I think that's something for the FDA to think about for both the observational designs going forward, but it is something that could be done better within a blinded crossover, and I think more successfully than if it's not blinded. But it is an incredibly important
question. We can get partial information out of it here better blinded, but not perfect. I think we're going to have to lean heavily on other designs as well.

DR. KURILLA: Thank you.

DR. MONTO: Final question. The other people who've got their raised, please circle back. We're going to have more discussion later. Dr. Rubin.

DR. RUBIN: Thanks. I'll echo what everyone else said, Dr. Goodman. Thank you for coming and speaking with us twice.

Of course, what you're arguing about is very compelling, particularly, I think, for the adverse events. I think we will learn something about that waning immunity from observational trials, but this really does preserve the ability to look AEs. And clearly, I think it's the way that they should have been designed.

But let me ask about the logistics of implementing it now, right now, for the Pfizer vaccine or Moderna, should it receive an EUA, people are
already getting a vaccine. And they're getting vaccine
in specific groups, so that high-risk groups are
getting it first. And we may already be losing those
people. So is it, do you think, going to be practical
to implement this design at this point?

DR. GOODMAN: So, as I mentioned, what this
does is it keeps the groups equal. So, yes, you might
lose preferentially, for example, all the healthcare
workers at the beginning. You'll lose them from both
the placebo arm and the vaccine arm in terms of the
blinded part. But then you have a period of time
before maybe the folks in the older risk groups, I
mean, there's a sequencing.

So you lose them sort of slice by slice. And
in terms of logistics, whether you do that on an
individual basis, or whether you plan it into the
trial. And you simply say, this strata will be crossed
over, you know, at 2.5 months after the two months of
observation of the placebo groups, the next one three
weeks later, the next one three weeks later.
So yes, you sequentially lose from the blinded part, not from follow up, the highest risk patients. But you can still learn a lot from those who are left. But the cohorts do change, but they stay comparable in the two arms.

DR. MONTO: Thank you, Dr. Goodman, and please stick around for -- what will be late morning for you -- for the discussion later on.

DR. GOODMAN: Okay.

DR. MONTO: Now, it's my pleasure to introduce representatives of the sponsor. We're going to hear from Dr. Tal Zaks and Jacqueline Miller from Moderna. Please.

SPONSOR PRESENTATION: EMERGENCY USE AUTHORIZATION (EUA) APPLICATION FOR MRNA-1273

DR. ZAKS: Good morning. Can everyone hear me okay?

MR. KAWCZYNSKI: Yes, sir. Go ahead.
DR. ZAKS: Okay. Thank you. Good morning.

My name is Tal Zaks, and I'm the Chief Medical Officer at Moderna. On behalf of myself and my colleagues, I'd like to thank the committee and FDA for the opportunity to present our data today.

We've carefully watched and listened to the meeting last week and, in preparing our presentation for today, we've attempted to proactively address many of the topics raised at that meeting and in the days that have followed. We have been developing our mRNA-1273 vaccine with a goal to seek global licensure for the prevention of the COVID-19 disease. And are here today seeking Emergency Use Authorization based on Phase 3 safety and efficacy data.

I don't need to belabor the damage this virus continues to wreck directly on our health and indirectly on our society and our way of life. Since the pandemic began, we at Moderna have moved rapidly to leverage the advantages of our mRNA platform. And we've been working closely with colleagues from the
National Institutes of Health to develop our vaccine. We've done so in a very transparent manner, sharing our Phase 3 clinical trial protocol as well as recruitment metrics with the public.

Let me briefly explain the merits of our vaccine. mRNA-1273 is based on messenger RNA, a molecule that is fundamental to the biology of every living cell and serves as the blueprint for all protein syntheses. Our vaccine uses our body's own cells to activate the immune system. It enables these cells to make only the part of the virus that is critical for the immune system to recognize: in this case, the spike protein.

Importantly, our vaccine platform has some inherent safety features: the mRNA does not self-replicate, does not enter the nucleus, and does not integrate into our DNA. The manufacturing process is cell free. It does not use products of animal or human origin, and it does not contain preservatives or...
adjuvants, thus avoiding some of the potential concerns of older vaccine technologies.

Now mRNA-1273 is not our first infectious disease vaccine. In fact, we've been in early phase clinical trials for the past five years conducting 12 clinical trials that have enrolled over 17 hundred healthy volunteers. SARS-CoV-2 is the ninth virus against which our mRNA vaccines have elicited neutralizing antibodies. And we have not seen a significant safety concern in any of our trials to date.

Since the company's inception, we've been investing heavily in understanding the critical quality attributes of our mRNA medicines. And we have been using these insights to continuously improve our process and manufacturing capability. We've leveraged this progress, at the start of the pandemic, to develop a product that remains potent and stable in cold chain shipping and storage conditions, that are widely available in hospitals, pharmacies, and assisted living
and skilled nursing facilities. At the point of care, mRNA-1273 can be deployed in a multiuse vial with no further mixing or dilution, while remaining stable for up to 12 hours at room temperature.

Our Phase 3 study, which is the basis of our presentation today, was conducted in collaboration with the NIH and in accordance with clear FDA guidance. It enrolled over 30 thousand participants, and we believe the results support Emergency Use Authorization. mRNA-1273 efficacy clearly exceed the recommendations for an EUA and eventual licensure.

The vaccine efficacy rate for symptomatic COVID-19 infection was 94.1 percent with a 95 percent confidence interval lower bound of 89.3 percent. These results are clinically meaningful and highly statistically significant. The efficacy observed is broadly consistent across all evaluated subgroups.

Importantly, we also observed a dramatic reduction in severe cases. All of the 30 severe cases observed at the time of primary analysis occurred in
people given placebo. A reduction in total symptomatic
cases predicts a reduction in cases leading to
hospitalization, intensive care, and death.

Finally, data from nine weeks of median
exposure in more than 15 thousand people vaccinated
with mRNA-1273 have well characterized the short-term
safety profile. We see generally good tolerability.
Most solicited injection site reactions and systemic
adverse events were reported as mild to moderate and
resolved quickly.

It is important to note, and to educate
people, that we see an increased rate of severity of
expected systemic symptoms like headache and myalgia
after the second dose. We view these as consistent
with a potent activation of a specific immune response.
They are transient and self-limited, and we do not see
a significant safety risk. These results support
acceptable benefit risks for broad population
vaccination to help prevent COVID-19 infections.
We acknowledge the need for longer term safety and effectiveness data. We will continue to transparently share our data, and the independent DSMB will continue to monitor safety as well as monitoring the duration of immunity and effectiveness. And we will continue to leverage the Phase 3 trial, even as we amend it to enable access to participants who received placebo.

Now, in this regard, we face some unique circumstances. First, as it relates to vaccine supplies, none of our trial participants would be quote/unquote jumping the line ahead of others, because we have clinical trial supplies available that, in fact, would expire and go to waste if we don't use them.

Second, all of our participants are at increased risk of infection, and many have risk factors for severe disease. One of the participants on our placebo arm died from COVID-19 during this trial. He
was a 54-year-old male whose sole risk factor was diabetes.

I'll defer to Dr. Baden to describe our proposed next steps on the trial, which will continue to be overseen by the DSMD and should provide significant additional data on both safety and effectiveness.

Now beyond the Phase 3 trial, Moderna will conduct additional studies in active pharmacovigilance to gain a more comprehensive understanding of the vaccine risk profile over time. We are initiating pediatric clinical trials, collaborating with the National Cancer Institute to evaluate the vaccine's safety and immunogenicity in people with cancer, and will continue to collaborate with FDA and other agencies to gather additional long-term safety data.

Here now is the agenda for the rest of our presentation. Let me now turn it over to Dr. Melissa Moore.
DR. MOORE: Hello. Good morning. My name is Melissa Moore, and I am the Chief Scientific Officer of Platform Research at Moderna. I'm also a professor in the RNA Therapeutics Institute at the University of Massachusetts Medical School.

Over the next few minutes, I will walk you through a description of Moderna's vaccine platform and, specifically, our COVID-19 vaccine mRNA-1273.

As the basis of our vaccine, we created a messenger RNA, or mRNA, that only contains the instructions to make the SARS-CoV-2 spike protein in a pre-fusion confirmation. We manufacture this mRNA in large quantities in a cell-free process that utilizes no ingredients of human or animal origin. We then formulate this mRNA with lipids to form lipid nanoparticles, or LNPs. As can be seen in the electron micrograph at the bottom right, our GMP manufacturing process yields a highly consistent product about a hundred nanometers in diameter.
In addition to the mRNA and lipids, the only other ingredients in the vial are water, sucrose, and two FDA-approved pharmaceutical buffers. Importantly, our vaccine contains no preservatives, no antibiotics, no adjuvants, and all components are rapidly cleared from the body. When our vaccine is entered intramuscularly, it is primarily taken up in the draining lymph nodes by specialized immune cells known as antigen presenting cells, or APCs. Once inside the antigen presenting cell, mRNA instructs the cells protein synthesis machinery to make the spike protein, which is then displayed on the cell's surface.

In the lymph node, this allows B cells and T cells to interact with the spike protein and develop an adaptive immune response. This adaptive immune response includes production of antibodies and the development of T cell responses against the spike protein, resulting in both humoral and cell mediated immune memory. Once the mRNA has done its job, it is degraded.
Importantly, our mRNA vaccine has no capacity to alter DNA. First, our externally delivered mRNA constitutes only a tiny fraction of all mRNA molecules in the cell. Second, our mRNA is transient and remains in the cytoplasm until eliminated by the natural mRNA decay process. To alter DNA, our mRNA would have to both gain access to the nucleus and be reverse transcribed. Our mRNA contains no signals for nuclear access and no known signals for reverse transcription.

Though in summary, mRNA-1273 directly educates the immune system by instructing antigen presenting cells to synthesize the SARS-CoV-2 spike protein. In this way, it efficiently drives an adaptive immune response by protein expression in situ. Finally, our mRNA can neither interact nor can it integrate into DNA. Thank you. I'll now pause and hand the presentation over to Dr. Jacqueline Miller to discuss mRNA-1273 efficacy.

**DR. MILLER:** Morning. My name is Dr. Jaqueline Miller, and I am the senior vice president
1 and therapeutic area head of Infectious Diseases at
2 Moderna. I'm pleased to share with you today some of
3 the details of our clinical development program in our
4 key immunogenicity and efficacy results. Before moving
5 to our clinical program, I would like to review our key
6 non-clinical results.
7
8 We generated an extensive non-clinical data
9 package in three different animal models including non-
10 human primates, or NHPs. Our data demonstrate that
11 mRNA-1273 induces humeral and cellular immunity,
12 including memory B cells in vaccinated animals. We
13 also challenged these animals with SARS-CoV-2 virus and
14 found that the vaccine could fully protect animals at
15 sub-therapeutic doses. No evidence of vaccine-
16 associated enhanced respiratory disease. We have
17 recently completed our developmental and reproductive
18 toxicology study which indicated no safety concerns.
19
20 Development of mRNA-1273 has been accelerated
21 given the COVID-19 pandemic. Nonetheless, a full
22 development program including Phase 1, 2 and 3 studies
have been executed. Study 101 was our Phase 1 dose-ranging safety and immunogenicity study conducted across three age strata: 18 to 55, 56 to 70, and over 71 years of age. Study 201 was a Phase 2 safety and immunogenicity study.

The primary focus of our presentation will be the Phase 3 COVID-19 efficacy and safety study, or 301, as it enrolled over 30 thousand participants, approximately 15 thousand of whom received mRNA-1273. Study 301 generated the vast majority of safety in all of the efficacy data.

So let's begin with the study 101. This slide summarizes the neutralizing antibodies induced by 100 micrograms of mRNA-1273 across three age strata. The shaded area represents a range of titers, from a panel of convalescent sera, taken from individuals recovering from COVID-19 disease. It serves as the clinical benchmark to compare immunogenicity between the doses and the (audio skip). Samples were collected from 23 to 54 days after diagnosis. Neutralizing antibodies
were induced in all participants by Day 36 for one week after Dose 2. GMTs were comparable across the three age strata including participants in the older age strata and persisted until day 119.

Now, let's discuss the T cell immunity evaluated in Study 101. CD4 T cells were further evaluated for Th-1 and Th-2 phenotypes since T cells are thought to associated with enhanced disease. The top panel of this slide represents the Th-1 phenotype, and the bottom panel is the Th-2. Th-1 dominant CD4 T cells are induced by Day 43 across age strata, minimal detection of the Th-2 phenotype. This analysis showed no evidence of enhanced disease.

I'd now like to present the immunogenicity results for the 100 microgram in placebo groups in Study 201. The dark blue bars represent the hundred microgram dose, and the gray bars represent placebos. By Day 43, there was more than a 50-fold increase in geometric mean titers in the vaccine group. And in the
placebo group, GMTs remained below the level of quantitation.

So, in summary, our Phase 1 and 2 studies showed the induction of neutralizing antibody titers in all participants by one week following the second dose. GMTs were observed to be higher than those of a panel of convalescent sera, and neutralizing antibodies persisted for three months after the second dose across all three age strata. Th-1 dominant CD4 T cell response was also observed across age strata and was consistent with our findings in animal models.

So now, let's look at the efficacy data from Study 301. Study 301 was designed to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 compared to placebo in adults at least 18 years of age who are at risk for COVID-19. Thirty thousand four hundred twenty participants were randomized one to one and received two doses: vaccine or placebo. Participants received the first dose on Day 1 and the second dose one month later on Day 29.
have been monitored for efficacy, immunogenicity, and safety endpoints throughout the study.

Immunogenicity endpoints include the measure of binding and neutralizing antibodies at the indicated timepoints. These immunogenicity samples will also be used to assess for asymptomatic zero conversion non-vaccine antigen. These data were not available for the emergency use submission and will not be discussed for today.

Efficacy surveillance occurred throughout the study. Once diagnosed with COVID-19, participants underwent daily telemedicine visits to ensure close medical follow up. Participants were also given pulse oximeters to manage their oxygen saturation daily.

Study 301 primary efficacy objectives were based on COVID-19 cases that occurred in SARS-CoV-2 sera negative participants that demonstrated success. The lower limit of the 95 percent confidence interval for vaccine efficacy had to be greater than 30 percent.
Secondary endpoints for vaccine efficacy include the evaluation of efficacy against severe disease and death, COVID-19 using the CDC case definition, and COVID-19 cases occurring after the first dose. There was also a secondary objective to evaluate asymptomatic SARS-CoV-2 infections, but the results are not yet available.

Please let me review the case definition for COVID-19 and severe COVID-19 disease. Primary efficacy endpoint were symptomatic, adjudicated COVID-19 diseases that occurred at least 14 days after dose 2. To be considered a case of COVID-19, a study participant had to have experienced at least two systemic symptoms, or at least one respiratory sign or symptom or clinical or radiographical evidence of pneumonia and confirmed SARS-CoV-2 infection from at least one naso- -- (audio skipped).

Study 301 also analyzed efficacy against severe COVID-19. Severe cases had to meet all criteria for the primary endpoint and have at least one of the
four following criteria: severe systemic illness; or respiratory failure, acute respiratory distress syndrome or evidence of shock; or significant acute organ dysfunction; or admission to an ICU or death.

To ensure adequate safety monitoring and to enable the interim efficacy analyses to this study has been monitored by a data and safety monitoring board or DSMB. DSMB was chartered and convened by the National Institutes of Health and is completely independent from the company.

In addition, an independent efficacy endpoint adjudication committee was assembled to determine if the case definitions for COVID-19 and severe COVID-19 were met. This committee has adjudicated all cases for the primary efficacy endpoints and continues to adjudicate cases as they accrue and will ultimately adjudicate all COVID-19 cases reported.

Thirty thousand four hundred twenty participants were randomized in Study 301 including 15,210 subjects to each group. The full analysis set
includes 15,181 participants who have received at least one dose of mRNA-1273. A modified intent to treat population includes participants who had no evidence of infection prior to receiving their first dose of study vaccine or placebo.

Per-protocol population was redefined for the primary efficacy analysis. It includes participants in the MITT who received both planned doses and had no major protocol deviations. More than 92 percent of participants vaccinated in both treatment groups are part of this population.

Now, let's return to the efficacy results. Enrollment was stratified to ensure that we studied participants most at risk for COVID-19. We pre-specified that at least 25 percent of our study population would include participants over 65 years of age or subjects between 18 and 65 with comorbid medical conditions. We were successful and enrolled a total of 42 percent of the study population in these two categories.
Let's review the study demography by gender and age. Approximately equal proportions of males and females participated, and the mean age was 51, the range of 18 to 95 years. Twenty five percent of the study population was over 65 years of age, and half of those individuals were over 70. Age and gender distribution were well balanced between (audio skip). This trial included approximately 10 percent African Americans, 5 percent Asian Americans, and 21 percent of participants who identified as being Hispanic.

This is the breakdown of the comorbid conditions reported in the study: 23 percent of participants overall reported at least one pre-existing condition. That included nine percent with diabetes mellitus, seven percent with severe obesity, five percent each with significant cardiac disease or chronic lung disease. A specific inclusion criterion was that participants had to be at increased risk for COVID-19.
Overall, 25 percent of our study participants are healthcare providers, and a substantial proportion of the remaining subjects meet the definition for essential workers, making together the participants depicted on this table represent more than 50 percent of our study population.

So here are the numbers of COVID-19 cases contributing to the primary endpoint by demographic subgroups. Thirty-three cases occurred in the elderly, including ten of the severe cases. Forty-two cases occurred in people from communities of color that have been disproportionately impacted by COVID-19.

This slide displays the primary efficacy results for the prespecified interim analysis. Primary efficacy hypothesis was met. Vaccine efficacy after the second dose was 94.5 percent with the lower limit of 86.5 percent. The difference between groups was statistically significant. The p-value less than 0.0001. The incidence rate in the vaccine group was 1.8 as compared to the 33.4 1000 person-years in the
placebo group. This interim analysis was submitted as part of Moderna's EUA application currently under review by the EUA.

A second analysis was performed when the full pre-specified cohort of 151 cases of COVID-19 had accrued, and the 2-months median follow up timepoint had passed. This analysis was predefined in the protocol as the primary efficacy analysis. There were 196 cases: 11 of which occurred in the vaccine group and 185 occurred in the placebo group. Vaccine efficacy was 94.1 percent with the lower limit of 89.3 percent. The difference between the groups was also statistically (audio skip). Incidence rate was 3.3 in the vaccine group compared to 56.5 in the placebo group.

Now, I would like to show you a forest plot of various subgroup analyses we performed on the primary endpoint stratifying the population by age, gender, race, and risk factors. All subgroup analyses were
consistent with the primary analyses, finding confidence to the generalized ability of the efficacy.

We also evaluated the efficacy of mRNA-1273 against severe COVID-19 disease, the secondary objective. Thirty severe cases have been adjudicated at the time of the primary efficacy analysis and all occurred in the placebo group resulting in a point estimate of vaccine efficacy of 100 percent. There's also a single death due to COVID-19 reported in the placebo group.

We have also evaluated efficacy according to the CDC's case definition, which required only one clinical symptom from an expanded list and a swab positive for SARS-CoV-2 virus. Point estimate of efficacy with this definition, 95.1 percent, which is highly consistent with the primary efficacy hypothesis.

We have also investigated that the efficacy against cases of COVID-19 which occurred 14 days after dose one as a secondary objective. There were 11 cases in the vaccine group compared to 225 cases in the
placebo group for an overall estimate of vaccine efficacy of 95.2 percent. The result is limited by fact that not all cases are adjudicated. More than 96 percent of participants received their second dose. The analysis included cases which occurred after the second dose. Nonetheless, the fact that the efficacy estimate is so consistent with the primary analysis is (audio skip).

The Kaplan-Meier curve, the cases that occurred in the modified intent to treat cohort since randomization are shown on this slide supporting the secondary efficacy analysis -- for efficacy after the first vaccination. Based on this, we also evaluated the percentage of subjects in the modified intent to treat cohort according to the CDC case definition which occurred after randomization. We'll see on the next slide.

So these are all the cases reported in each group stratified by two-week intervals up to the second dose. Overall, prior to 14 days Post-Dose 2, there
were 62 cases in the placebo group as compared to 8 cases in the vaccine group. Most of the cases in the vaccine group were reported in the first two weeks after vaccination. Taken together, these analyses suggest that protection may begin prior to Dose 2, but, for maximum protection, both doses should be given.

Our protocol specified analysis on the efficacy against asymptomatic infection was not available at the time of the EUA submission. However, it did collect Pre-Dose 1 and Pre-Dose 2 swabs for SARS-CoV-2 virus and has performed a descriptive summary comparing the number of positive swabs as a way to estimate asymptomatic infection.

Among baseline negative participants -- 14 in the vaccine group and 38 in the placebo group -- had evidence of SARS-CoV-2 infection at the second dose without reporting symptoms. There were nearly two-thirds fewer positive swabs in the vaccine group as compared to the placebo group at the Pre-Dose 2
So, in conclusion, mRNA-1273 has demonstrated clear and compelling evidence of vaccine efficacy against symptomatic COVID-19 disease. Vaccine efficacy was 94.1 percent, the lower limit of the 95 percent confidence interval of 89.3 percent successfully meeting the primary efficacy hypothesis and exceeding the FDA guidance for COVID-19 vaccine.

At the time of the data cutoff, 30 cases of severe COVID-19 had occurred in the placebo group, and no cases had occurred in the mRNA-1273 group. Efficacy against severe disease is reassuring about the lack of enhanced disease, and participants in this trial will continue to be followed for breakthrough disease.

All key secondary sensitivity and subgroup analyses were consistent with primary analysis underscoring the performance of the vaccine across high-risk populations. Given this high and consistent
efficacy, mRNA-1273 offers the potential to address the public health crisis of COVID-19.

Thank you. I'd like to invite Dr. David Martin, the head of Pharmacovigilance at Moderna, to discuss the safety data.

DR. MARTIN: Good morning. My name is David Martin, and I'm the vice president of Pharmacovigilance at Moderna. I will review our safety results from Study 301 whose vast study represents 97 percent of total mRNA-1273 vaccine exposures.

I will present the nine-week median exposure follow up data using the same November 25th data cutoff as the primary efficacy analysis. This provides 6,579 person-years of safety data. It represents 20 percent more follow-up time than previously available in our EUA submission, which was based on a seven-week median. Let's take a look at the Study 301 safety data.

More than 30 thousand participants were enrolled and received at least one dose. In both groups, compliance with getting a second dose was high.
About 97 percent of participants received the second dose. As of the data cutoff, more than 60 percent had complete two-months follow up.

Now moving to the data. Beginning with solicited adverse reactions captured for the entire population. Overall, there were more solicited reactions reported in the mRNA-1273 group than in placebo with a consistently higher occurrence after the second injection.

Here are the data for solicited local adverse reactions after the first injection. As you can see, the most commonly reported was pain. Eighty-seven percent of participants in the mRNA-1273 group aged 18 to under 65 and 19 percent of the same age range in the placebo group experienced pain. In participants 65 and older, 74 percent of the mRNA-1273 group and 13 percent of the placebo group had pain.

Similar patterns but much lower rates were seen for erythema, swelling, and axillary swelling or tenderness. Overall, these reactions were mostly mild
to moderate in severity represented by the dark green shading, Grade 1, and the lighter green shading, Grade 2. Grade 3 reactions shown here in orange occurred at lower rates. There were no Grade 4 events reported. Overall, solicited local reactions were short lived with a median duration of one to three days.

A similar pattern was seen for solicited local adverse reactions after the second injection, and, again, the most commonly reported was pain. A higher percentage of participants in the mRNA-1273 groups experienced these symptoms with an increase after the second injection compared to the first. Again, Grade 3 reactions occurred at low rates, and no Grade 4 events were reported.

Here, we're looking at solicited systemic adverse reactions after the first injection. Fatigue, headache, myalgia, and arthralgia were the most commonly reported, and they were mostly mild to moderate. Grade 3 reactions occurred at a low rate, and Grade 4 were even lower. The Grade 4 reactions
aren't visible because they were reported in 0.1 percent or less in both groups. These reactions were also short-lived lasting a median of one to two days.

Here are the data for solicited systemic adverse reactions after the second injection. As you can see, there is an increase in Grade 3 reactions after the second injection in the mRNA-1273 groups. Again, the Grade 4 reactions occurred at very low rates. Overall, most reactions were still mild to moderate and resolved within one to two days.

I'll now review the unsolicited adverse events. Unsolicited adverse events reported in the overall stage of the trial were comparable between groups. Six deaths occurred in the mRNA-1273 group, and there were seven deaths in the placebo group.

This figure depicts medically attended adverse events by system organ class. These too were comparable between groups and the rates were low.

Here we see serious adverse events by system organ class. These were comparable and infrequent with
no terms reported in more than 0.25 percent of participants.

Deaths were balanced between groups and were assessed by investigators as not related to mRNA-1273.

This slide shows solicited adverse reaction rates after any dose by baseline SARS-CoV-2 status subgroup. Rates are shown for local adverse reactions on the left and systemic adverse reactions on the right. These data indicate that individuals who were positive at baseline for SARS-CoV-2 did not experience higher rates of solicited adverse reactions and baseline serum negatives.

We have actively scrutinized our safety data to identify and analyze possible cases of anaphylaxis. We found no cases suggestive of anaphylaxis to mRNA-1273. It's important to note that participants with a history of anaphylaxis, urticaria, or other significant hypersensitivity were not excluded from Study 301.

There were two anaphylactic reactions reported as unsolicited adverse events: one in placebo and one
in the mRNA-1273 arm. The placebo event occurred ten
days after the first dose. That was attributed to co-
administration of radiocontrast dye, and the
participant received the second dose of placebo.

The mRNA-1273 event occurred 63 days after the
second dose in a person with a history of asthma and
allergy to shellfish. We also ran the anaphylaxis
Standardized MedDRA Query and reviewed events that
occurred within 48 hours of vaccination. None met
Brighton Collaboration Anaphylaxis Case Definition
criteria. Of course, we will continue to actively
monitor for these events.

I'll now review our safety monitoring
activities for the post-authorization period. Moderna
works hard to develop an integrated vaccine monitoring
system that complements U.S. government and other
established programs and is focused on identifying
safety signals as rapidly as possible.

This system has three goals. One, to monitor
for adverse events of special interest and other
concerns associated with vaccines in general. We will of course, look for AESI patterns in VAERS, but we will also actively monitor AESI in real-world healthcare data as I'll explain in a moment.

With respect to safety in the event of vaccine exposure during pregnancy, a developmental and reproductive study was completed in December 2020 with no adverse findings. Given the limited human exposure to date in the Phase 3 trial, we will establish a pregnancy registry that includes a cohort recruited from the general population.

Our second broad goal is to monitor long-term vaccine effectiveness through a study in an integrated healthcare delivery system.

Third, we will identify and assess unanticipated safety signals as rapidly as possible. Again, by monitoring adverse event reports from the U.S. and from other countries. But, in addition using real-world healthcare data, we can add any
unanticipated safety signals to the vaccine monitoring
system as I will describe.

Given the recent events in the United Kingdom, we know that an active surveillance system using a large data source is critical to capture rare adverse events. We will identify expected rates of AESIs prior to vaccination using a cohort of 45 million adults from a large, linked healthcare claims data source. In this scaled visual, you can see how the sample, with women in red on the left and men in blue on the right, closely matches the U.S. population. This cohort complements but does not duplicate the large electronic health data surveillance systems operated by the FDA and the CDC.

Next, to capture observed rates of adverse events post-vaccination, we will follow new vaccine administrations providing data updates every two weeks. This is will enable analyses comparing observed to expected rates. We will also include linked open claims data for early visibility on vaccination that
can be connected to subsequent adverse events. In addition to AESI, we can rapidly add new safety signals to this monitoring program for assessment.

In conclusion, I'd like to point out that collaboration is key to a successful global vaccine safety monitoring program in a world-wide pandemic. Moderna's global pharmacovigilance and risk management plans are currently being reviewed by the FDA as well as by international regulatory agencies. We will interface with vaccine safety stakeholders to learn from their safety signal detection programs and to share their information. These will include the U.S. FDA and CDC, as well as international regulatory and public health agencies. Working together, we can enhance public confidence in the vaccine through robust collaborative safety monitoring.

I will now turn the lectern over to Dr. Lindsey Baden who treats COVID-19 patients and will share his clinical perspective on the ongoing Phase 3 trial.
DR. BADEN: Can you hear me?

DR. MARTIN: Yes, we can, sir.

DR. BADEN: Thank you. So I'm Dr. Lindsey Baden. I'm a physician and investigator at Brigham and Women's Hospital in the Dana-Farber Cancer Institute. I'm an associate professor of medicine at Harvard Medical School, a medical journal editor, and one of the three co-principal investigators of this trial.

As co-principal investigator of this study, I am funded by the NIH for this work. I have received no funding from Moderna. I share my views, but they are informed by many discussions with colleagues at NIH NIAID, CoVPN, Moderna, study PIs, site staff, and study participants, among others.

The efficacy data from the two large, well-done Phase 3 trials are compelling and are not lost on many of our study participants. How many more severe illnesses in the placebo group will we have -- and we have about two to three per week -- do we need to convince ourselves of the short-term efficacy? It's
important that we carefully consider the volunteer's viewpoint as we navigate fairness, equity, trust, transparency, as well as the larger societal interests. Without them, clinical research cannot function.

We have a unique obligation to handle this study properly as these are likely the last large-scale data from a high-quality, randomized allocation process. Future observational work will be invaluable but will have methodologic issues that require challenging analytics to get correct.

There are many ethical challenges in trial conduct, and a quarrel one is that study volunteers should not be disadvantaged. Principles of research require our informing participants of new information, such as a clinically available 95 percent effective vaccine, especially one that can prevent severe illness. By doing this, we build trust in research broadly. We need to communicate with our study participants in a clear and understandable manner. They are intelligent and informed.
They will vote with their feet. We are currently -- since the EUA authorized last week -- having substantial dropout from study participation given the increasing availability of vaccines. This dropout undermines the data integrity and what can be learned. We must be proactive to ensure that the best choice is for our participants to remain in the study. They will continue to make sacrifices for us to gain knowledge as they have done, but we must ensure our ask of them is reasonable and respectful. This requires moving with haste and ensuring that are treated fairly.

Should those who are more health and health system savvy and vocal be treated differently than those who are more passive in the process? The study enrolled rapidly, especially in Caucasian and healthcare provider communities. Given efforts to enhance diversity, participants enrolled later in the study were from more diverse communities.
Should the communities earlier in the study be treated differently than those communities enrolled later in the study? A majority of those in this trial, as already mentioned, would fall into CDC priority Groups 1a through c. These numbers on this image need to be interpreted carefully as Groups 1a and b are mutually exclusive, but they are not with Group 1c. In any case, this reminds us that the majority of our volunteers have substantial risk for suffering significant health consequences from COVID-19.

Maintaining the volunteers in the research trial, not just for the next few months but for the next 18 months, is of value. To this end, my Moderna colleagues, as Dr. Zaks mentioned earlier, have informed me -- us -- that they have residual research-labeled vaccine product due to expire soon which could be used for an open-label crossover redesign of this study. This vaccine product is unlikely to be available for any other purpose given timing and regulation.
This next image shows -- well, there are many possible paths forward including maintaining the original double-blind design for at least six months, unlikely to be successful due to volunteer dropout; a double-blind crossover; and an open-labeled crossover as seen in this image.

I want to comment a moment on the double-blind crossover. As Dr. Goodman raised at in some detail -- and that is my favored design, and I am a co-author on that paper and have discussed it extensively with Dr. Follmann and others, as we have thought about redesigning the path forward since efficacy data emerge from the DSMV meetings a month ago. The problem is it's impractical at this point in time in my view. And, if we lose our volunteers, then the ability to learn anything further will be substantially impaired. So we must carefully consider the merits and risks of the different paths forward, but we do have to choose a path forward, one that, hopefully, builds participants
and trust and enables us to gain more knowledge as to how these vaccines work.

So, in this image, as a pragmatic path forward, what one sees is reconsenting of all volunteers, informing them of the new EUA associated information, obtaining a serology -- this exit serology -- from the double-blind RCT component of the study will allow us to make an assessment of the vaccine on asymptomatic and subclinical infection. We need high compliance with this data point.

At this time, the volunteer can choose to stay in the study as designed: double-blind placebo controlled or crossover to an open-label format with placebo recipients being now being vaccinated. All will be followed as per the original study design including assessments of safety, immunogenicity, and efficacy.

All will continue in a randomized research study, so research continues. This is not clinical application. This is a continued research study.
evolving to an open-label format from a double-blind format in the volunteers in our early versus late vaccine recipients which will allow systematic knowledge to being gained, including a potential identification of a correlate of protection. By using vaccine research supply, there was no impact on clinical EUA vaccine deployment.

Of note, about two-thirds of volunteers would make it to the six months of double-blind, placebo-controlled follow up in March. Crossing over to an open label format in the next month or so would lose about two months of volunteer blinded follow up. We must carefully balance the value of collecting data from a double-blind format with the ethics and participant interests which will translate into study retention or loss to follow up and the impact on data and knowledge that can be gained.

In the proposal on this slide, all volunteers are treated fairly and equally. The research enterprise continues to build and maintain the trust of
our community, and society gains knowledge. The proposed design balances obligation to both the volunteer and society. Next image please.

We must continue to learn from those who are in this RCT and are four to six months ahead of the rest of us. There are many more questions over the next months to years that these volunteers can help us answer but only if they stay in the study. If the volunteers leave the study, particularly for non-random reasons, then future knowledge will be fundamentally undermined. I would like to now turn the lectern back to Dr. Zaks.

DR. ZAKS: Thank you, Dr. Baden.

DR. MONTO: I just wanted to let you know you're already over time.

DR. ZAKS: I will briefly conclude. Thank you. In conclusion, the data from Study 301 supports the Emergency Use Authorization, and we expect the data to support sure licensure. The safety and reactogenicity have been well characterized and will
continue to be characterized as these occurred both on trial and using passive and active surveillance during real-world deployment.

I am grateful for the ongoing collaboration with the NIH and the clear and timely guidance of FDA, and we look forward to the opportunity to prevent COVID-19 with mRNA-1273. We also appreciate the efforts of this Committee for reviewing our data, and we look forward to answering your questions. Thank you for your attention, and I will turn it to Dr. Miller to moderate the Q and A session.

DR. MONTO: I think -- Dr. Miller, I think I'm the one who's supposed to be moderating the Q and A session.

DR. MILLER: No, absolutely. I'm just helping out with coordinating on our side.

DR. MONTO: Okay. Thank you. It won't be very much time to do it right now. We have just a few minutes for the start of the Q and A.
I just want to remind everybody that the open public comments is a fixed part of this meeting. We'll start at noon Eastern time and go on for an hour. We also need to have a short break before that time especially for technical reasons. So we can only have a couple of questions now. We'll circle back. I'm sure you will all remember the questions that you have stored and have the question session starting at 1:00 Eastern. So a couple of question now. I see many hands raised. I'll just do the first few right now, and we'll put the rest of them off until 1:00. Dr. Offit.

DR. OFFIT: In the 11 breakthrough cases, you showed data that you clearly have sera that were collected following Dose 2. So what I'm trying to understand is the characteristics of those 11 cases. I mean, it may be that there's immunological correlate infection, which Dr. Baden correctly said. It would be really important to know, so it would be great to have
those data. But it sounds like you don't have them yet. Is that true?

DR. MILLER: That is correct although we expect them in January.

DR. OFFIT: Okay. And then was there anything else about those 11 patients, any characteristics of them that distinguish them from those who were protected by the vaccine?

DR. MILLER: Nothing in particular, Dr. Offit.

DR. OFFIT: Okay.

DR. MILLER: These were cases that were split relatively evenly given the small sample size between males and females: three were Hispanic, eight were white and non-Hispanic; and they ranged in age from 29 to 72.

DR. OFFIT: Okay. Thank you very much.

DR. MONTO: Dr. Gans.

DR. GANS: Thank you very much. Thank you for all of those illuminating presentations. I had a
couple of questions, and one was a continuation of the breakthrough cases that Dr. Offit had raised. Not only humoral immunity or our trying to understand the correlates of protection as he suggested, I noticed one of my questions -- and it all moves to the breakthrough -- is that T cell immunity was only evaluated. Actually, it looks like not in the Phase 3, and I don't know if those samples are also being included and particularly relevant to the breakthrough disease.

My other question, which you can either handle now or later, is what about other adverse events like Bell's palsy, which we did note of interest because that seems to be a signal not only with this vaccine but the other one.

**DR. MILLER:** Thank you, Dr. Gans, for those two questions. And maybe I'll address your second question first. So, given the review of last week, we have looked carefully into the data. We have four cases of Bell's palsy that have been reported: three of
them occurred in the vaccine group, one of them occurred in the placebo group. And this will be part of our post-marketing safety surveillance.

So, in addition to continuing to monitoring through the Phase 3 trial, as the vaccine is, hopefully, authorized for EUA and expanded, this will be one of the key safety endpoints that we will be looking for in our signal detection.

And then your question about the T cell immunity, so indeed our T cell work was done in collaboration with the NIH in our Phase 1 clinical trial. And, in terms of looking for a correlate of protection, so our search for a correlate has focused up until now on the neutralizing and binding antibody responses. So you mentioned the breakthrough cases that we've observed will go towards that analysis, and, as we continue to accrue data in the trial, additional breakthrough cases will be added to that analysis.

The samples in the Phase 3 trial, as they require very special handling for T cell immunity and
as we were implementing across a hundred U.S. sites, the T cell immunity was not part of what we instituted in Phase 3. So the correlate work that we're collaborating with the NIH on we're really focused on the binding and (audio skip).

DR. MONTO: Dr. Moore.

DR. MOORE: Thank you. So also I want to really thank you for presenting the data even though it was interim data on the asymptomatic infections because I just feel that's so strongly important for control of this epidemic, and it could determine wide-spread use of one vaccine versus another vaccine. Although asymptomatic infection is a surrogate measure for transmissibility, it's a commonsense measure of transmissibility or shedding at least.

So, if you break blinding, do you anticipate re-swabbing all the participants beforehand, and do you -- what are your plans for a second swab? I know that you measured them right before your second dose. Is
there plans for having another nasopharyngeal swab from these patients -- from these participants?

**DR. MILLER:** Thank you for that question. So you're correct that it was the predefined swabs at both Pre-Dose 1 and Pre-Dose 2 that enabled us to be able to do that analysis. And a pretransition swab could certainly be implemented into the Phase 3 study.

The way we predefined our surveillance for asymptomatic infection was actually through serology against the anti-nucleocapsid protein, so it's a serologic evidence of immunity to non-vaccine antigen. But, to your point, swabs really add a lot of important additional data.

Some further data that were not available at the time of the EUA also include swabs we obtained frequently from subjects who were found to be COVID-19 positive. So the intent there is really to look at the viral shedding and the burden of shedding comparatively between groups, so we should have some additional data on some of that.
DR. MONTO: Thank you. Dr. Hildreth.

DR. MOORE: Can I just a question? If you sequence that virus, do we have any idea of whether there's virus escape antigen that escape from when you vaccinated?

DR. MILLER: So we are deep sequencing the virus as part of the surveillance of the breakthrough cases, and I am going to ask Dr. Darin Edwards from our --

DR. MONTO: Can we -- have time for exactly one more question. We'll circle back to -- I'll call on you again to answer the sequencing and the breakthrough question, which is a very big one. Dr. Hildreth, your final question.

DR. HILDRETH: Yes, I was concerned about the lower efficacy in the older age group, and I wondered if you had some thoughts about addressing that either with a higher dose or an additional injection? Any comments about -- thoughts about that?
DR. MILLER: Yes, to speak about the older age group, I want to mention -- and let me bring up this slide -- that that efficacy was really based on the relatively small sample size with a wide 95 percent confidence interval. So the confidence interval completely overlaps with the confidence interval for the overall efficacy.

You can see that that was based on 33 cases. If you were to evaluate efficacy in the those above 75 years of age -- so at even greater risk -- there were 7 cases, all of which were reported in the placebo group, and I think it highlights -- I mean, it certainly is very helpful to look at all of these subgroup analyses to ensure that we're not seeing dramatic differences. I think we do have to keep in mind that there weren't multiplicity adjustments for the multiple endpoints. And so our view is actually that the efficacy in the elderly is indeed consistent with the efficacy in the overall population.

DR. HILDRETH: Thank you.
DR. MONTO: Thank you all. Thanks to Moderna, and don’t forget you have to come back to answer our questions at 1:00. Now, we have a break until the open public hearing which starts at exactly noon Eastern time.

[BREAK]

OPEN PUBLIC HEARING

MR. KAWCZYNSKI: Alright. Good afternoon and welcome back to our meeting. We will now get started with our OPH session. Now, I'll pass it back off to our chair, Arnold. Dr. Monto, do you want to take it away?

DR. MONTO: Okay. Welcome to the open public hearing session. Please note that both the FDA 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, its product, and if known its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, 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 the issue of financial relationships, at the beginning of your statement, it will not preclude you from speaking. Over to you Prabha for leading the open public discussion.

**DR. ATREYA:** Good afternoon everyone. Thank you for joining us today. I'm going to read out your
name one after another. When I call your name, please start speaking. And when you finish, please mute your phone so that we can call the next person. Thank you so much.

Speakers you have only three minutes and there is a timer that indicates three minutes for your remarks. Thank you. Okay. The first name is Dr. Winston Wong. Go ahead, please.

**DR. WONG:** Thank you, Madam Chair, for the opportunity to provide public comment. My name is Winston Wong, and I am the Chairperson and acting CEO of the National Council of Asian Pacific Islander Physicians. I have no relevant financial disclosures to share.

I speak on behalf of our national council, that was formed 10 years ago to provide an advocacy voice for physicians who are actively committed to the healthcare needs and public health needs of vulnerable Asian Pacific Islander and Native Hawaiian communities. Technical assistant, could you please go to the next
slide which shows the logo of the National Council of
Asian Pacific Islander Physicians?

In this context, the impact of COVID-19 on the
AANHPI community has been underreported. Its impact on
our community mirrors that of other communities of
color. And could you go to the next slide which talks
about the under-reported story of COVID-19 burden on
Asian Americans?

For example, according to a recent report from
the Kaiser Family Foundation, derived from electronic
health records from 52 million patients across 32
states, Asian Americans were less likely to get tested
for COVID, more likely to have a positive test result,
and require a higher level of care at diagnosis.
Moreover, they were more likely to be hospitalized and
die compared to all other racial, ethnic groups
according to the EPIC data that I referenced. Against
this sobering backdrop, NCAPIP greets the news of the
Moderna vaccine with cautious optimism.

Our communities need the protection offered by
the promise of our vaccine. It's provision to the AANHPI community must incorporate critical components that are both relevant and unique to our population.

I'd like to go to the next slide, which starts with the title critical issues in vaccine deployment for our community.

Therefore, our organization recommends, number one; this aggregating data for the broad category of the AANHPI in efficacy and potential adverse vaccine effects, in recognition that this category is comprised of dozens of subgroups and important differences can be lost when data is not broken down. Can I have the next slide which has the numeration of Asian Americans?

As the vaccine is deployed, the immigration status of Asian American individuals should not be a barrier for access. Although the vaccine itself may be free of charge to U.S. residents, the special status of individuals from the Pacific jurisdictions such as Micronesia should be accounted for. Can I go to the next slide?
As the Moderna vaccine is deployed, every effort should be made to provide information about its background in a culturally competent and linguistically accessible manner. Since many AANHPI individuals travel to and from Asian countries, and also obtain information about COVID-19 from sources other than those that originate in the mainstream and or American press, efforts should be made so that there is no confusion or misinformation about an individual's vaccine status.

Number four, physicians and other clinicians from Asian American, Native Hawaiian, Pacific Islander communities like those at community health centers should be supported as critical ambassadors that advocate for the Moderna --

MR. KAWCZYNISKI: Time.

DR. WONG: -- and other COVID-19 vaccines.

Thank you for allowing me this opportunity to comment on the important issues relative to the Asian American, Native Hawaiian community as we look forward to the
approval of the Moderna vaccine.

DR. ATREYA: Thank you. The next speaker is Ms. Lisa Butler.

MS. BUTLER: Hello. My name is Lisa Butler, Executive director of the GBS/CIDO Foundation. At this time I have no financial interest or conflicts of interest to disclose. Thank you to the FDA for this opportunity.

Guillain-Barré Syndrome is an acute inflammatory disorder of the peripheral nerves. GBS is characterized by the rapid onset of numbness, weakness, and often paralysis of the legs, arms, breathing muscles, and feet. The paralysis is ascending. The cause is unknown. We do know that about 50 percent of cases occur shortly after a microbial infection, viral or bacterial, some as simple and common as the flu or food poisoning. Many theories suggest an autoimmune trigger.

The COVID-19 pandemic sparked a flurry of anxiety for healthcare professionals and former GBS
patients. Our community waited eagerly for the news of an increase of GBS cases being triggered by COVID-19 infection. Fortunately, despite a handful of GBS cases happening around the time of COVID-19 infection, there has not been any indication of an increased risk of GBS from a COVID-19 infection.

A recent study out of the U.K., published in the Brain Journal of Neurology this week, confirmed that there is no epidemiological association between the COVID-19 and GBS in the U.K. The resulting commentary from the published article highlighted the opinion of leading peripheral nerve experts, that there should not be any increased risk of GBS from the COVID vaccine. Please see the chart on the slide.

In 1976, there was an apparent association between the influenza vaccine and GBS. However, since then several studies have researched the risk of GBS after influenza vaccinations and have no, or a very small, increase in the risk of someone contracting GBS after influenza vaccine. And this finding was recently
highlighted by an article from CBER, CMS, and the Immunization Safety Office of the CDC.

Additionally, leading peripheral nerve experts remain confident that any GBS cases resulting from mass COVID-19 vaccination of the global community are coincidental and likely in line with the expected rate of GBS. Regardless of the science though, the GBS community expresses understandable skepticism towards vaccinations. A safe and effective vaccine against COVID-19 served as a beacon of hope for many Americans, but the Guillain-Barré Syndrome community feels a renewed sense of worry and panic at the news of this expedited scientific miracle.

Though the data is still quite limited, the Foundation’s Global Medical Advisory Board and the Peripheral Nerve Society are hopeful that the relative risks of GBS after a COVID-19 infection is not significant, and that there is no reason to suspect that the vaccine would cause it. The Foundation urgently hopes for a partnership with the FDA to
collaboratively and truthfully instill necessary and earned trust in the GBS community regarding vaccinations, especially the COVID-19 vaccinations.

We will continue to rely on experts who serve the Global Medical Advisory Board at the Foundation for their assessment of science and safety. So in conclusion, we are a very nervous patient community, yet we are very optimistic for the future. Thank you for your interest.

DR. ATREYA: Thank you, Ms. Butler. Next speaker is Dr. Diana Zuckerman.

DR. ZUCKERMAN: Hi. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Next slide, please. We scrutinize the safety and effectiveness of medical products and we don't accept funding from companies that make those products. My expertise is based on post-doctoral training in epidemiology, as a former faculty member and researcher at Vassar, Yale, and Harvard, and a former Fellow in Bioethics at Penn. I've also worked at HHS and
Congress. Next slide, please.

I'll focus on three concerns. Number one, the two-month median follow-up is too short so Moderna's proposal to immediately unblind and offer to vaccinate the entire placebo group should be rejected. Number two, Moderna recruited a diverse group of participants, but only four COVID cases were Black, and even fewer were in other racial groups. We can't assume that the vaccine was highly effective in demographic groups with so few cases. And there were 25 cases among participants with comorbidities, which is slightly more substantial.

Number three. I'm glad to see that, unlike Pfizer, Moderna provided a total number of participants who reported one or more adverse events. That's important. Unfortunately, the total of severe, systemic adverse events, after the second dose, was over 17 percent for the vaccine group compared to 2 percent for placebo. Next slide.

There were 30 severe COVID cases after the
second dose, none in the vaccine group. This is a strong finding. Nine required hospitalization but 12 were based on the questionable criteria of at least slightly low blood oxygen saturation. Next slide.

Long-term care patients were not included in the study. And 1,300 people over 75 were in the study but only three were cases. We want to save their lives, but with no data it's not possible to provide useful, informed consent to nursing home patients. That puts a tremendous burden on those patients and their family members. Next slide.

We need longer-term data on benefits and risks. The vaccine is clearly effective but does it last two months, or four months, or a year? To learn that, the FDA needs to ensure the blinded RCT is continued. Last slide, please.

In conclusion, FDA should initially target authorization to priority populations. If the EUA is given for all adults, celebrities and others who are well connected will cut in line. We've already seen
that. (audio interruption).

-- other people could apply for the vaccine under FDA's expanded access program. We need at least one year of blinded, randomized control data. I agree with Dr. Goodman's proposal that FDA should delay access to vaccines, by placebo group members, unless they are in priority populations. Blinded crossover is better than not continuing a blinded controlled study if that's the only alternative. Thanks so much for the opportunity to speak today.

DR. ATREYA: Thank you. Next speaker is Dr. Charles Lee.

DR. LEE: Good morning. I am Dr. Charles Lee. Next slide, please. I represent the American College of Correctional Physicians and I am speaking on behalf of correctional workers and those who are incarcerated. There are no conflicts.

Just look at the numbers. There are 2 million people incarcerated in the United States and 500,000 workers working within correctional facilities. The
infection rate amongst those incarcerated is six times that of the general population. 1,700 folks have died. Why so many? There's an inability of inmates to follow the CDC guidelines. Why? They cannot socially distance. They are unable to get proper hand sanitizers because of the alcohol content. They live in close-dorm quarters or cells. There's an inability to get frequently tested. There's poor ventilation. Many of these facilities are 18th, 19th century, and they may not get masks. I realize that this varies from facility to facility.

There are increased inmate vulnerabilities. An inmate has a physiologic and medical age of 20 years younger than that of the general population. Someone 50 incarcerated, his body equates to that of someone 65 on the outside. There are increased percent of minorities within correctional facilities. There's a significant increase of patients who have comorbidities, diabetes, asthma, cardiovascular disease.
There's also increased vulnerabilities of workers. Out of necessity, they have close contact with inmates. They have extremely demanding working conditions. Unfortunately, too many officers may get sick, thereby unable to properly manage the facility, increasing the danger within a correctional facility.

What are the consequences of this? Increased deaths, suicidality. There have been fears of patients that they may die of Coronavirus committing suicide. As a result of this, there's increased community infections. Ninety percent of inmates are released at some point in time, workers go home daily. There's increased use of community resources, clinics, emergency rooms, hospitals. When patients who are incarcerated become sick, they are referred to the community resources.

The Moderna vaccine has certain advantages that may be extremely applicable to correctional populations. As a result, the American College of Correctional Physicians recommends approval of the EUA
for Moderna's vaccine. Thank you very much.

**DR. ATREYA:** Okay. Thank you, Dr. Lee. The next speaker is Dr. Bisola Ojikutu.

**DR. OJIKUTU:** Thank you for this opportunity to speak. My name is Dr. Bisola Ojikutu and I have no financial disclosures. I am an infectious disease specialist and a frontline provider based in Massachusetts, which has one of the highest death rates from COVID-19 in this country. I work at Brigham and Women's Hospital and Massachusetts General Hospital, and I've been working directly with Black community members for the last few months to promote acceptance of the COVID-19 vaccine, as many of us have.

Many of the community members that I've worked with have suffered personal losses secondary to COVID-19, so this is a particularly important issue to them. Next slide. In this process of working with the Black community, I have attended numerous town halls and had many meetings and discussions, and I think it's really important to emphasize that mistrust of government and
of the pharmaceutical industry runs deep. And though the recent polls show that willingness and acceptance may be increasing, we still believe that the mistrust will delay and even completely inhibit uptake of these vaccines.

While it's highly unlikely that we will make our institutions more trustworthy over the course of the next few weeks as vaccines are rolled out, I and others believe that the same amount of effort and funding that was placed in the development of this, and other successful vaccine candidates, needs to be directed toward ensuring uptake and promoting vaccine confidence, specifically within Black, Latinx, and indigenous communities who are most disproportionally affected.

What do we need to do? First, we need better messaging articulated by trusted messengers that will resonate with racially and ethnically diverse individuals. Second, we need more intensive community engagement. Though I'm well aware of several
initiatives that, quite frankly, recently just got started, what has been done thus far is nowhere near enough. Next slide.

In terms of messages, first, we need complete transparency, in lay language, regarding potential side effects, and we need to be honest and emphasize that there are many unknowns, and much work remains to be done. Secondly, our government institutions and industry need to consistently acknowledge that systemic inequity and structural racism have led to this deeply rooted mistrust. Thirdly, we need to reframe vaccination as a form of empowering our communities in fighting back against COVID-19 related inequity.

And lastly, we need to explain this process, this process that we're part of today, to our communities. People want to know who was looking out for them and their best interest and the interest of people who look like them, and who was really at the table. Next slide.

And in regard to the table, quite frankly,
communities of color have not been at the table throughout the entire vaccine development process. They were not engaged early enough, and that is a problem. Going forward, we must change that dynamic. People of color will begin to trust this process, and the process of other vaccine development, if they feel that they're truly part of it. Therefore, community engagement and community investment must be enhanced, amplified, and fully supported. I believe that this is necessary or we will continue to see racial and ethnic disparities and we will not end this epidemic. I'll stop there. Thank you.

DR. ATREYA: Thank you. The next speaker is Dr. David Berger.

DR. BERGER: Thank you. Hi, my name is David Berger. Thank you for the opportunity to address this committee again. I have no conflicts of interest. Slide two.

I'm a board certified pediatrician and senior medical advisor for the Vaccine Considerations Project.
Slide three. From the available data, it appears the Moderna and Pfizer vaccines are quite effective in minimizing the incidence of serious COVID disease. This is an amazing scientific accomplishment that will hopefully aid in our defeat of the virus. Slide four.

Vaccine hesitancy is prevalent in the healthcare community and public at large. Full transparency can reduce this hesitancy. As more manufacturers apply for authorizations, I urge the FDA to provide timely information for review. Meaningful input is not possible when we are given only two days to review manufacturer's data before addressing the committee, or when data is released after deadlines pass for submission. Slide five.

Seniors are one of the first targeted populations to receive COVID vaccine, yet only 860 subjects over 75 years old were included in the reported Pfizer data. Moderna's data mentions subjects over 55 years old but made no distinction of participants over 75 years old. Our team found minimal
data on pregnant women or those with preexisting allergic, hyperinflammatory and autoimmune conditions. If this data's not available, it will be very difficult for individuals to weigh the risk and benefits, which is fundamental to making an informed decision. As with the Pfizer vaccine, Moderna's report reveals incidents of Bell’s Palsy. While the number of cases was a small fraction of participants, we should closely monitor this to see if the trend develops for this and other inflammatory conditions. Slide six.

Please provide long term data and outcome for patients with or who may develop autoimmune and hyperinflammatory conditions. Significant symptoms may take longer than two months to become evident. Please provide quantitative standards for COVID IgG antibodies, so people can determine if they have immunity and if their immunity is persisting. Slide seven.

Our team have not discovered significant differences in efficacy or adverse events between the
Pfizer and Moderna vaccines. We will continue analyzing and commenting on other manufacturers as they apply for emergency authorization. It will be helpful to have comparative data to guide the decision making process between brands. Slide eight.

The Vaccine Considerations Project is building a central repository of COVID vaccine health and safety concerns. Our national network of medical and graduate students are compiling and analyzing science, data, and evidence-based information to help address these concerns. We are inviting all interested students, professionals, and others to join this important effort by connecting with us at vaccineconsiderations.com. Slide nine.

It is critical that rigorous safety mechanisms are maintained and we are given complete transparency with data. We should closely monitor and report on unique subpopulations, such as different minority and racial communities, the elderly, and those with allergies, autoimmune, and hyperinflammatory
conditions. With such actions, the FDA and vaccine manufacturers have the opportunity to provide Americans the information they need to make the most informed decision possible for themselves and their loved ones. Thank you.

DR. ATREYA: Thank you, Dr. Berger. The next speaker is Dr. Renu Dhanasekaran.

DR. DHANASEKARAN: Thank you very much. Thank you very much for the opportunity to speak at this public hearing. My name is Renu Dhanasekaran. I'm a board certified gastroenterologist and hepatologist at Stanford University, California. I am here as a physician to advocate for vaccine access for my patients and also as a scientist conducting COVID-19 research. I have no conflicts of interest to disclose. Next slide.

COVID-19 is a global public health crisis. It has led to more than 1.5 million deaths in the world with more than 290,000, unfortunately, occurring in the United States alone. Next slide. Patients with
chronic medical conditions like cancer, heart disease, and obesity experience worse outcomes with COVID-19.

As a physician taking care of some of the sickest patients with chronic liver diseases and immuno-compromised patients with liver transplantation, I have personally seen the devastation COVID-19 has caused for our patients both directly and indirectly. Hence, clearly, the vaccine is a welcome relief for our elderly patients and those with chronic medical conditions. Next slide.

As discussed by the earlier speakers, the Moderna vaccine has been shown to be effective in preventing COVID-19. When I looked at the data, I was happy to see that among the 30,000 participants in the Phase 3 COVE study, around 7,000 were older than 65 years, around 5,000 who were younger than 65 years had underlying medical disorders like diabetes, obesity, and cardiac disease. Overall, around 42 percent of the cohort consisted of medically high-risk groups. This is reassuring to me. These are the very patients who
are in dire need for this vaccine. Next slide.

Moving on, I would like to acknowledge a sad reality that communities of color have been disproportionately affected during COVID-19. The CDC reports that American Indians, Blacks, and Hispanics are at more than 2.5 times the risk for death with COVID-19 than white Americans. Several investigators, including us, have shown that socioeconomic factors and medical comorbidities play a huge role in this. Next slide.

I'm happy to see that the COVE study cohort overall included 11,000 people from communities of color with more than 6,000 Hispanic and more than 3,000 Black. I believe these vulnerable communities will benefit greatly with the Moderna vaccine approval. Next slide. I have reviewed the safety profile of the Moderna vaccine, the vaccine was generally well tolerated as can be seen from the Grade 3 events listed here. In my opinion, the benefits far outweigh the risks with the vaccine, especially in patients with
comorbidities. Next slide.

I would like to end with these two take-home points. Number one, a safe and effective vaccine is the need of the hour. Number two, vulnerable populations will be especially well served with vaccine approval. Next slide. Thank you very much for the opportunity to speak.

DR. ATREYA: Okay. Thank you Dr. Dhanasekaran. The next speaker is Dr. Marie Garlock.

DR. GARLOCK: Warm greetings. I am Dr. Marie Garlock. I'm a board member of the U.S.A. Patient Network. We're a grassroots patient advocacy group and we're not funded by or beholden to industry in any way. We're completely independent. Hundreds of members across the nation, like me, were patient caregivers of leading health justice advocates for drug and device safety, efficacy, and affordability.

Our letter submitted to the federal docket today has references for all four of our main concerns and action items. And I'd like to say before we move
to the next slide titled, "EUA is Stopgap not a Stand
In," given recent project on government oversight
reporting I want to start with a note. Unlike at last
week's EUA hearing, today's deliberation must take time
to transparently include all expert members' questions,
voting amendments, and explanations. Today is not
about PR, it's to take public health seriously, a
commitment on which the FDA leadership must make good.
So the next slide titled, "EUA is Stopgap not a Stand
In."

Clinical trial must continue. Here is the
basic part of it, do we want to control COVID-19, then
we have to keep the control groups going. Anything
less skirts accountability for industry and FDA. We
need public trust in COVID-19 vaccines that will only
come from transparent public knowledge about how they
work long terms, when, and for whom.

What does that mean? Placebo groups much
continue alongside Phase 4 trials. We need metrics
that matter. Does the vaccine prevent transmission?
Does it mitigate severity of disease that results in hospitalizations and death?

Next, we need to incorporate the National Vaccine Injury Compensation Program. Folks can go to hrsa.gov/vaccinecompensation. And then we need for health-focused media, elected officials, FDA and Moderna, and its peer industries to know that EUAs are not standard FDA approvals and authorizations. We need transparency on that. And an EUA should not ever be precedent for future similar, or unrelated drugs and devices, to be rushed through on loopholes. And next slide.

We need transparency on diversity. So this means for age and comorbidities. Because this population is so vulnerable, how many are at or near 75 years old? How many are frail elderly, i.e. older and with comorbidities? On sex and reproductive health status, we need to understand that females should know they should not get pregnant for a specified time after getting the vaccine, given lack of data on both
developing fetuses and pregnant parents. And most of all, we need to understand for ethnic and racial difference.

Given systemic racism as the root of COVID-19 health disparities, we need precise numbers for Black, Indigenous, Pacific Islander, Latino, and Hispanic folks. And in order, those folks in comparison to their white counterparts, Indigenous, Black, Pacific Islander, Latino and Hispanic people are three times as likely to die from COVID-19, and four times as likely to be hospitalized with severe COVID-19.

In a framework called structural competency, we know systemic racism influences these upstream inequities in employment, housing, transportation, parallel health challenges, and healthcare insurance coverage. And that is directly reflected in COVID-19 severity, hospitalizations, and deaths. So we need nuance on the numbers and we need retainment of these specific groups in placebo groups for Phase 4.

Most of all, FDA needs clinical trial
diversity standards that have a systemic fix. We commend Moderna for showing its trial recruitment, but it should not be only optional for companies. And our next slide.

MR. KAWCZYNSKI: Time.

DR. GARLOCK: Okay. Thank you so much. And I would like to ask the FDA to focus on needing nuance on the numbers, keeping the control groups going, knowing that integrity requires adverse event reporting infrastructure, and that action means action. The FDA must ensure safety in these protection practices.

Thank you.

DR. ATREYA: Okay. Thank you. The next speaker is Ms. Gwen Schell.

MR. KAWCZYNSKI: Gwen, do you have your personal phone muted?

MS. SCHELL: Sorry about that. My name is Gwen Schell. I represent a community of rural population. I'm a nurse and I work for a public health district. I want to describe the impact that COVID-19
has had on the rural population and touch on the value of a vaccine.

We have very limited nursing staff in this part of the United States. And in a rural population, that nursing staff is covering an area of about 500 miles. We have noticed an uptick in people being sent home from the hospital who are not meant to be home. All of the local assisted living and skilled nursing facilities are very particular about who they take. A vaccine would not only benefit those who are at risk for contracting COVID-19, but would also benefit the health population at large.

I wish to express our excitement and gratitude for treatments that are coming. And I forgot to mention, I don't have any financial ties. But I just wanted to bring to light the impact that a vaccine will have on rural populations. Thank you.

**DR. ATREYA:** Thank you, Ms. Schell. Next speaker is Dr. Douglas Dieterich.

**DR. DIETERICH:** Thank you. I’m Dr. Douglas
Dieterich. I'm the Director of the Institute for Liver Medicine at Mount Sinai Health System and a Professor of Medicine at the Icahn School of Medicine at Mount Sinai.

I'm here as a patient actually, not as a professor, even though COVID-19 causes significant liver disease and significant mortality in patients with preexisting liver disease. I think it's important to recognize that there is a space between life and death. We see the deaths which are extraordinary, 3,600 yesterday, and the number of people infected.

I was infected in mid-March as was about two-thirds of my clinical team. I was hospitalized for about a month and sent home on six liters of oxygen. Subsequently, I discovered that I had severe peripheral neuropathy in my feet and severe fibrosis, pulmonary fibrosis, which I'm still getting treated for actually both of them. And of course my sense of smell is completely gone. So I think it's important to recognize that as good as our treatment is now,
prevention is clearly much better. There's a lot of long-term effects of COVID.

After I was at home for a few months I developed some severe atrial arrhythmias. When they subsided, I've developed severe hypertension which I'm still battling. And of course, I'm still taking medicine so that I can feel my feet and hopefully recover some of my sense of smell.

So I think the important thing is that there's a real price to be paid for getting COVID, whether it's severe or not. There are long-term side effects. And I think that the vaccine is the answer to prevent COVID-19 and not to get it, and get treated, as good as treatment is nowadays.

In addition actually, even though my antibody levels remain extremely high, I will get vaccinated when my time comes. I think that's an important thing to recognize as well.

I wanted to thank the Moderna people and the other vaccine makers for helping us prevent this
Thank you for the opportunity to speak.

DR. ATREYA: Thank you. The next speaker is Dr. Jasmine Marcelin.

DR. MARCELIN: Yes. Thank you very much. My name is Dr. Jasmin Marcelin and I'm an infectious diseases physician in Nebraska. I am employed by the University of Nebraska Medical Center, but my comments do not represent my employer and I have no conflicts or disclosures to report.

After reviewing the available information about the mRNA vaccine, developed by Moderna, I am encouraged by the 94 percent effectiveness demonstrated and review of expected adverse effects. I would advocate for continued long-term monitoring of clinical trial participants to evaluate for the long-term effectiveness and safety. However, I am encouraged for this vaccine to receive EUA status with prioritization of those at highest risk.

We still do need data regarding pregnant
people and children, and hope that there will be more sharing of outcomes of people who become pregnant during the trial period. I know that there were 36 percent of participants in the trial from communities of color, and few reported cases from these participants. Considering how and what we know about the disproportionate rates of COVID-19 in Black and Brown communities, I urge vaccine discussions to avoid centering mistrust of the Black and Brown communities as originating within those communities, and instead acknowledge the fact that the healthcare profession has previously betrayed these communities through centuries of structural racism, including grievances that are happening today.

So, therefore, we need to have open listening and understanding of the concerns of these communities. And trusted healthcare professionals from communities of color need to be engaged to ensure that the approach continues through a lens of equity and cultural congruence.
I would also comment on the importance of funding campaigns with appropriate messaging and community engagement in the rollout, to emphasize safety and efficacy for laypeople to encourage vaccine confidence, and appropriate messaging about expected side effects so as not to alarm people when they occur.

And then finally, hoping for an equitable distribution plan that ensures that people in rural, low income and communities of color have adequate access to the vaccine, including follow up for second injections. Thank you for the opportunity to participate in this open comment and I'm looking forward to seeing what the vaccine has to do for the community in the future. Thank you.

DR. ATREYA: Thank you. The next speaker is Dr. Robert Wong.

DR. WONG: Hi. Good afternoon. I have no conflicts or disclosures. Dear committee members, thank you for giving me an opportunity to speak today and share my thoughts on the importance of timely and
equitable implementation of this COVID-19 vaccine. My name is Robert Wong. I'm a Clinical Associate Professor of Medicine at Stanford and a practicing gastroenterologist and hepatologist serving our U.S. Veterans at the VA Palo Alto Healthcare System in Northern California.

In addition to my clinical practice, which focuses on management of patients with complex liver diseases, my clinical research is focused on healthcare disparities, particularly among ethnic minorities, vulnerable populations, and underserved safety net health systems. Even prior to the COVID pandemic, ethnic minorities and vulnerable populations suffer significant healthcare disparities. From receiving timely screening and surveillance exams to delays in access to life-saving treatments.

Specifically, for patients that I serve, my research has demonstrated disparities in timely receipt of high-quality liver disease care, including access to viral hepatitis treatments for patients with chronic
Hepatitis B and Hepatitis C, as well as timely screening for liver cancer among cirrhosis patients. In the past nine months, since the pandemic began in the U.S., we have seen these disparities exacerbated as our chance to deliver high quality care has been disrupted by this pandemic. Patients avoiding care due to fear of venturing out to medical visits for labs or imaging for cancer screening, also healthcare systems transitioning to telehealth delaying non-urgent procedures. And trying to balance the risks of delaying diagnostic and treatment procedures with the risk of our vulnerable patients being exposed and infected with SARS-CoV-2.

These vaccines that are now before us present some hope at the end of this deadly year, where many of us have lost not only patients but close friends. While these vaccines will not be the magic bullet, that miraculously reverses all the damage this pandemic has caused, it gives us hope that one day in the not too distant future some semblance of normalcy will be
within our reach.

While I have no doubt in the eventual approval and dissemination of these vaccines, I would like to encourage all of us to be particularly cognizant of ensuring equitable access, particularly among those underserved and vulnerable populations whose existing healthcare disparities have been disproportionately exacerbated by this pandemic. Thank you all very much for taking time to hear my comments.

DR. ATREYA: Thank you, Dr. Wong. The next speaker is Dr. Joseph Bick.

DR. BICK: Good morning. My name is Joseph Bick and I'm an infectious diseases specialist serving as statewide director of healthcare services for the California Department of Corrections and Rehabilitation. I have no financial disclosures to report.

I appreciate the opportunity to speak to the committee regarding the importance of including those who work and reside in our jails, prisons, and
detention centers in the first phase of COVID vaccination. Over 2 million people are incarcerated in this country. Over 500,000 individuals interact with them on a daily basis as correctional officers, nurses, cooks, respiratory therapists, physicians, teachers, and others.

More than 260,000 inmates and 58,000 correctional employees have been diagnosed with COVID resulting in at least 85 employee and 1,700 inmate COVID-related deaths. The age-adjusted death rate due to COVID among the incarcerated is several folds higher than what is seen in the outside community. And case rates among both inmates and employees are significantly greater than those seen outside incarcerated settings. Many of the largest COVID outbreaks in this country have occurred in correctional facilities.

Many facilities do not routinely test for COVID, and therefore these numbers underestimate the true burden of COVID in these settings. Most inmates
are housed in large, overcrowded congregant living environments in which consistent physical distancing is not possible. Many of these settings suffer from insufficient ventilation and hygiene, contributing to the likelihood of widespread COVID outbreaks. Inmates are disproportionately people of color, and often they have multiple comorbidities that increase their risk for serious illness, hospitalization, and death if they become infected with COVID.

Delaying vaccine distribution to inmates will exacerbate the disparate racial impact of COVID-19. Advanced age is one of the greatest predictors of poor outcome of COVID, and age-associated risk for prisoners begins to rise in their 50s. The average age of inmates in this country has risen significantly over the years. Currently, over 10 percent of prisoners are 55 years of age or older. Many of our prisons are essentially nursing homes, long term care facilities, and skilled nursing facilities with bars. Jails, prisons, and detention centers are
often a major employer in some rural settings. When employees unknowingly introduce COVID, the disease can be rapidly amplified and subsequently fuel large outbreaks in the outside communities. Inmates who require hospitalization can quickly overwhelm bed capacity in surrounding community healthcare facilities.

Cases among staff and inmates are currently surging to unprecedented numbers threatening to overwhelm local resources. Not including correctional staff and high-risk inmates in vaccination Phase 1 will result in preventable illness and deaths, burdens upon local economies, unsafe jails and prisons, and increased pressure upon over-stressed community hospitals. In closing, I urge you to include high risk inmates and front-line correctional workers in phase 1a for this and all future COVID vaccines. Thank you.

DR. ATREYA: Thank you, Dr. Bick. The next speaker is Dr. Donald Middleton.

DR. MIDDLETON: Hi. I'm Don Middleton, a
professor of family medicine at the University of Pittsburg School of Medicine. I am unofficially speaking to support EUA approval of the Moderna mRNA vaccine, which has shown its worth in rigorous blinded clinical trials. I do serve on a Moderna mRNA vaccine advisory board. My background is in vaccine education and I am one of the developers of a free vaccine app for iPhones and Androids called “Shots,” by AAFP/STFM. COVID-19 is ubiquitous. It's in the air, on doorknobs, on computers, in the trash. Even when social separation policies are followed to the fullest, infection still occurs. The number of infected persons is staggering, the number of deaths more so. In the U.S., 300,000, a number that is difficult to grasp. Basically, the city of Pittsburg wiped out.

As we have already heard, recovery from COVID often takes months or is incomplete. Most days when I walk into UPMC Saint Margaret, my true home, a community hospital with about 200 beds, I wonder how many COVID patients do we have. Is this the day, is
this the one when I will become infected?

Others who work here share that fear, but it
does not stop thousands of our hospital employees from
doing their jobs. Our hospital staff always keeps in
the forefront that the patient is a person, something
the statistics fail to convey. Before November we used
to have a few, maybe five or seven COVID in-patients
daily. Now we have 60, sixty out of 190 in-patients.

One day this week, 9 out of the 10 patients in
the ICU had COVID, and seven were on respirators. A
70-year-old woman on a respirator had to communicate
with handwritten messages. Just before being sedated
to improve her oxygenation, she scribbled a note to the
outstanding resident doctor taking care of her, "I
love y'all. My life is in y'all's hands." A heart
with an arrow through it was attached to the bottom of
this note.

Endless lights, noise, strangers in the rooms,
not loved ones, everyone is gowned and mask. You
cannot really sit to talk with patients or hear their
fears. Even though the staff does their duty daily, they are working in hell. Control of COVID requires vaccine, billions of doses. The Moderna vaccine offers real hope that this pandemic can be truncated. And with published evidence of lasting immunity, help to keep it permanently at bay. Please advise the FDA to give this outstanding vaccine full EUA status. Thank you very much.

DR. ATREYA: Thank you. The next speaker is Mr. Sidney Wolfe.

DR. WOLFE: Good morning. I'm Dr. Sidney Wolfe, Public Assistance Health Research Group. I have no conflicts of interest. During the October 22nd meeting of this committee before seeing data from either Pfizer or Moderna vaccines, FDA's Dr. Doran Fink pointed out that, "Deployment of a weakly effective COVID-19 vaccine could result in more harm than good. It could do so by providing a false sense of security that interferes with measures to reduce SARS COVID transmission, such as wearing of masks, other PPE, and
social distancing."

I would argue that, even with current evidence that both vaccines are highly efficacious, there is still understandable concern about the danger of a false sense of security, if those getting vaccinated no longer adhere to proven preventative public health measures such as wearing masks and appropriate social distancing. The FDA's 2017 EUA guidance include a requirement for an FDA-approved patient fact sheet to accompany the use of all EUA products, "...to ensure that recipients are informed about the product they receive, and to inform them of any available alternatives to the product and of the risk and benefits of available alternatives."

Since 2017, no EUA for a vaccine had been granted prior to the Pfizer vaccine, but providing written information about proven health measures, such as wearing masks and appropriate social distancing, is clearly necessary and appropriate for COVID vaccine recipients. Flashing back to last week, less than 24
hours after the EUA for the Pfizer vaccine was granted, the FDA posted a Pfizer fact sheet for recipients and caregivers intended for recipients of their vaccine. The fact sheet accurately states the Pfizer-BioNTech vaccine may not protect everyone.

Unfortunately, it contains no mention of the need for wearing masks and appropriate social distancing. For further information, the fact sheet suggested asking the vaccination provider or your local or state government health department, and then lists websites that do not state such preventive measures should accompany vaccination. Though necessary as a part of company's EUA submissions, such fact sheets were not included in briefing packages provided to the public or possibly the advisory committee for either today's or last week's advisory committee meeting.

But this morning, Dr. Doran Fink mentioned that FDA's review yielded -- FDA mentioned that the review and revision of fact sheets, for vaccine recipients, were part of what happened when FDA looked
at the EUA submission. So this is at least mentioned in today's meeting which it hadn't been before.

I hope your advisory committee urges that important public information, such as that, must immediately be added to vaccine fact sheets before millions more people are vaccinated. Thank you very much and I hope you will ask the FDA questions about this. It does not seem to be in their presentation for this afternoon. Thanks again.

DR. ATREYA: Thank you, Dr. Wolfe. Next speaker is Dr. Roberta Luskin-Hawk.

DR. LUSKIN-HAWK: Thank you. I'd like to thank you for the opportunity to comment on today's deliberations. My name is Dr. Roberta Luskin-Hawk and while I'm employed by Providence Saint Joseph Health, I am speaking as a private citizen today. And I have no relevant financial disclosures.

I'm an infectious disease physician with extensive experience in conducting and analyzing clinical trials, in addition to experience in
overseeing healthcare delivery across both urban and rural settings. My current role, as Hospital Chief Executive serving remote area of Northern California, provides a unique perspective on the potential impact of emergency use authorization of mRNA 1273 COVID vaccine on rural communities.

A current surge in COVID-19 is having a devastating impact in communities across the country, and the demand for care is starting to exceed capacity in parts of the U.S. healthcare system, with further increase in cases forecasted in coming weeks. While the numbers of patients with COVID-19 in rural communities may seem limited, even small numbers of cases, or illnesses among healthcare workforce, can threaten the fragile healthcare infrastructure and limit the ability to provide critical care to people in these communities.

This intervention is needed, and we are fortunate to have had a robust response from the scientific community. It is therefore essential that
we rapidly deploy vaccines that are found to be safe and effective against SARS-CoV-2 to both rural and urban communities across our country. The data provided on the Moderna mRNA 1273 COVID vaccine demonstrates exceptional vaccine effectiveness in the reduction of symptomatic COVID-19 across all ages, in addition to beneficial impact on the severity of disease. The vaccine also seems to have a favorable side effect profile in early evaluations.

Use of the vaccine with this efficacy will not only save lives that could be lost to COVID, but will help relieve ICU capacity available for the care of patients with other acute medical conditions. The fact that storage requirements can be met by healthcare organizations, without access to ultra-low temperature freezers, will have an added benefit to many small, rural hospitals and clinics.

Vaccination of 21 million U.S. healthcare workers and vulnerable populations is urgently needed to protect our healthcare workers, our healthcare
infrastructure, and to change the tide of the pandemic. Rapid and broad distribution of vaccine will require EUA and eventual approval of more than one safe and effective SARS-CoV-2 vaccine.

I urge you to provide Emergency Use Authorization for mRNA 1273, which has met the necessary safety and efficacy benchmarks in the analysis of the clinical trial data. I personally believe that this approval is needed to support our healthcare workers and to save lives. Thank you.

DR. ATREYA: Okay. The next speaker is Ms. Veronica Halloway.

MS. HALLOWAY: Good afternoon and thank you for the opportunity to speak today. My name is Veronica Halloway, Chief of the Center for Minority Health Services at the Illinois Department of Public Health. I have no conflicts of interest. I want to recognize Dr. Damon Arnold who has been leading community conversations and education about COVID-19 vaccine on behalf of Illinois' COVID-19 Equity Task
To ensure that disparately impacted rural and urban communities of color are informed and engaged in the process of building trust, raising awareness, promoting the importance of vaccination, and creating equitable access and distribution, we launched several initiatives. We engaged with a diverse group of community partners including faith-based, people with disabilities, the homeless, refugee and immigrants, returning citizens, seniors, and the LGBT communities to discern a need for special assistance.

We launched a community ambassador's program to ensure confidence with directed messages surrounding COVID-19 vaccinations. These conversations made clear that education and targeted communications regarding misinformation and rebuilding trust, vaccine science, and active collaboration with communities are key. Accurate timely information, concerning the safety and efficacy of the vaccines from the manufactures and scientific community, is vital.
National and state data shows that COVID-19 kills more males than females, and Black males already have a life expectancy 8 to 11 years shorter than their white counterparts. Special outreach efforts should be made to engage Black males in order to improve participation in both outreach and vaccine uptake. Messaging must be consistent with community beliefs and perceptions about the vaccine.

We convened two meetings to collect perspectives from communities mentioned. We noted that both cultural and linguistically-appropriate language is essential for effective communication and delivery of quality healthcare. Providers appear to require additional training with respect to cultural norms and implicit bias. Providers must be intentional about truly engaging with local gatekeepers and community members about the vaccine. The current COVID-19 pandemic also underscores the need for a more diverse healthcare workforce reflective of the communities they serve.
In closing, there is concern that the access and distribution of vaccines will encounter hurdles within already negatively impacted rural and urban communities of color. Federal, state, and local support is needed such as additional funding to support the use of tools, like COVID-19 Community Vulnerability Index, which combines the CDC's Social Vulnerability Index with epidemiological and health system factors, to target areas most likely to be impacted. Thank you for your time and attention to this important matter.

DR. ATREYA: Thank you. The next speaker and the last speaker of the session is Dr. James Woody.

DR. WOODY: Hello. I'm Dr. James Woody and I'd like to thank the FDA for the opportunity to speak. I have no financial disclosures. I'm a pediatric immunologist and a biotech executive, who in a prior life discovered and developed a drug called Remicade. I'd be interested in how patients on anti-TNF inhibitors do with your vaccine. But that's not why I'm here.
I talk about what I see as the optimal format for deploying a COVID vaccine for the Navy and the Marine Corp. My comments are my own and do not reflect in any way the opinion of the Navy or Marine Corps. So I'm a retired U.S. Navy Captain who spent 20 years in the U.S. Navy as a medical officer. I ran worldwide Navy medical R&D. One of our jobs was to be aware of any infectious disease risk anywhere in the world where a Navy ship might port, or personnel go into conflict.

By way of experience, as a former commanding officer of the Navy's medical unit, NAMRU-3 a BL-3 force facility in Cairo, Egypt for four years, my team of about 50 Navy people did surveys for infectious disease over the entire Eastern Africa and Mid-East region. And they included HIV, Hepatitis, Ebola, Congo-Crimean, Rift Valley Fever, Lasa, and serious stuff.

So as you know well, space on Navy ships is very confined and berthing space is always limited, so transmission of infectious diseases is a concern. We
have actually shut down ships in the past due to chickenpox outbreaks.

As you have seen on the press, over 190 Navy ships have had COVID cases, representing about 65 percent of all Navy ships at sea. Likewise, the Marine Corps recruits who live in congested facilities have also had significant numbers of COVID cases. So should the Marines be required to deploy on ships, which is the usual sequence, the overcrowding will be even worse, and they'll even be at higher risk.

So assuming a two-dose schedule will work to provide protective immunity, so what's the best format for use by the Navy and Marine Corps? Common sense needs to prevail here. Simple is better. Available storage, no diluting.

So in situations where multi-doses are required, the smaller shore-based clinic facilities, and the shipboard facilities, must have similar kinds of storage equipment and capacity, so that once a Seaman or Marine is deployed with a first dose, they
can actually get a second dose that can be administered anywhere onshore or in the fleet.

So most shore-based facilities have the usual -20 degree home-type refrigerator/freezer, so vaccines could be stored in any of these locations and the second dose be administered quite easily. Use of the much lower temperature specialized freezing, at -70 or 100, is not a reasonable option as such kinds of equipment is only available on very few, very large ships, or in shore-based hospitals.

So in summary, from someone who's actually been in the trenches, common sense needs to prevail here. Simpler is better. Thank you very much for the opportunity and listening to my talk.

**DR. ATREYA:** Thank you, Dr. Woody. I would like to thank all the OPH speakers at this point for making the comments. This concludes the open public hearing session. And then now I would like to introduce Dr. Peter Marks. He wanted to make his thanks as well. So, Dr. Marks are you ready?
DR. MARKS: Thanks very much. So thank you very much to our public speakers. I just want to take a moment, before we move on to the further questions and then FDA presentation and then deliberations later on. There wasn't an exact perfect time to thank everyone today, but this may be a reasonable one just to thank everyone for their participation.

This is somewhat of a historic events to have these two advisory committee meetings so close together. And we really thank all of the advisors for taking the time to go through a very large amount of material. Also need to thank our FDA staff who have worked tirelessly, going through an amazingly large amount of material over the past weeks. And that was only made possible because they had worked for several months with the companies internally, and with stakeholders to prepare things so that this relatively rapid EUA review would be possible.

So incredible thanks to our FDA colleagues and thanks for all who are tuning into this process. I
also need to call out the advisory committee staff
which has done a remarkably great job in putting
together this meeting. So I won't hold us up anymore
and I'll turn this back to Dr. Monto.

DR. ATREYA: Thank you, Dr. Marks. Dr. Monto,
the floor is yours.

ADDITIONAL Q&A FOR SPONSOR PRESENTERS

DR. MONTO: Thank you very much. We're going
back to questions directed to the sponsor. And I see
Dr. Miller's ready and I'll re-address the question. I
interrupted when we broke, and that was about escape
mutants and what you're going to do about them,
sequencing, and the rest.

MR. KAWCZYNISKI: Jacqueline, you have your own
phone muted.

DR. MILLER: Thank you for the reminder that I
was still muted. Apologies for that. So thank you,
Dr. Monto. Yes, indeed. The question actually was
about whether we were intending to sequence the samples we receive from breakthrough cases. And the answer is, yes. We are in the process of deep-sequencing virus from those cases. And I was going to invite Dr. Darin Edwards, who is the head of our pre-clinical group, to address the work that we have been doing to assess the effectiveness and immunogenicity of the vaccine against emergent mutants. Dr. Edwards?

DR. EDWARDS: Thank you for that. Thank you, Dr. Miller. In addition to deep-sequencing of cases in our Phase 3 trial, we're also performing additional research assessments. These include the evaluation of vaccinated, either animal or human sera, the ability of that sera to neutralize these breakthrough, or these variant strains. We're also additionally monitoring for additional strain variance, both through our own internal efforts as well as through collaborations with external research partners.

We have thus far identified five strain variants that are of key concern. And we have, at this
point, assessed both mouse and non-human primate sera that were vaccinated with mRNA 1273 to protect against these strain variants, and we see they equally protect. In the future we are also performing assessments on human sera. Thank you and I hope that addresses your question.

**DR. MONTO:** Thank you. Let’s go on to Dr. Sawyer. I believe you have a question.

**DR. SAWYER:** Thank you. And thanks for the great presentations. Given our new and unexpected focus on anaphylaxis, I just wanted to ask if you've seen anaphylaxis in any of the other -- I believe you said eight -- vaccines that you had previously developed and given to a quite small number of people? Whether you've seen allergic hypersensitivity reactions in any of your animal models? And whether you have done, or are planning to do, any in vitro studies to see if this mRNA lipid platform creates interactions that would predict allergic-type reactions?

**DR. MILLER:** Yes. Dr. Sawyer, thanks for that
question. And indeed, we have been doing a very rapid review of our overall clinical database in light of the information that has come forward about the other mRNA vaccines.

So as you mentioned, we do have a clinical database across eight other vaccines. It includes approximately 1,700 recipients of a similar lipid nanoparticle with specific mRNA sequences. In those cases, we've had one other report of anaphylaxis. It was a woman with soy allergy in more than a few months outside of her vaccination.

And I should clarify that although participants have been excluded on the basis of a known allergy to one of the components of the vaccine, we have not routinely excluded participants who have a history of allergies or anaphylaxis. And then your second question was about potential in vitro studies. In fact, Dr. Zaks has been in discussion actually with thought-leaders at the NIH, BARDA, and so forth to talk about what additional activities we might collaborate
to better understand what this potential (audio fades).

    DR. SAWYER: Thank you.

    DR. MONTO: Dr. Lee.

    DR. LEE: Yes. I had a question about the unblinding. A number of people indicated that there is a clinical trial supply that could be used for that purpose, and that would not interfere with any supplies that would be given, say, to the general public if the EUA were to be granted. So my question is, what -- the indication was that it had a limited shelf life. And I think my first question, related to that, is how long do you think that supply will last? And related to that is would you have enough doses to vaccinate in two doses, for all 15,000 placebo participants, were they all to ask to do that?

    DR. MILLER: Thanks for your question about the vaccine supply. And yes, it is true that we have sufficient supplies to be able to vaccinate our placebo participants. The supply actually will be expiring relatively soon. So by the end of the next month, the
supplies will be expired, so they cannot be used for
emergency use.

DR. LEE: Great. Thank you.

DR. MONTO: Dr. Cohen.

DR. COHN: Hi, Dr. Miller. Thank you. I was
wondering if you could give us a little bit more
information about -- I can't remember if you said three
or four cases of Bell's Palsy, including how many days
after vaccination symptoms started to occur and how
long symptoms occurred, and if those persons recovered.
And if they have a history of Bell's Palsy?

DR. MILLER: Thanks for that question, Dr.
Cohn. So the cases occurred between 17 and 32 days
after vaccination. They were either resolved or
resolving at the time of this presentation. And they
were -- three were non-serious, one was a serious
adverse event.

DR. MONTO: Dr. Kurilla.

DR. KURILLA: Thank you. Dr. Miller, in terms
of your efficacy evaluation, you began counting two
weeks after the second vaccine dose. But your Kaplan-Meier curve between vaccine and placebo begin to diverge after about two weeks after the first dose. But your immunogenicity in your Phase 1 say that even by two weeks, after the first dose, there's no neutralizing titers, and there doesn't seem to be any bump in T-Cells, which suggests that there's some kind of non-specific antigen, vaccine-mediated protective effect potentially going on.

And the question becomes, how long does that actually manifest, and do you know what that is? With reactogenicity, I would presume it's inflammation and interferon, and K-Cells and that sort of thing. I'm just wondering how much that might be bleeding into the primary efficacy endpoint analysis?

DR. MILLER: Yeah. Thanks for that question. So we did show a difference in the reported cases in the Kaplan-Meier curve after randomization, as you mentioned. We do know that our vaccine induces innate immunity with the first dose, and the adaptive immunity
clearly increases the second dose. Understanding this phenomenon a bit further is why we looked into that one dose efficacy in several different ways.

So looking at it in terms of the time period when the mRNA 1273 cases might be reported, as well as looking at the PCR swabs and looking at the ability of the -- or the differences between the vaccine and placebo groups in terms of that positivity.

So I am also going to ask Dr. Melissa Moore if there's anything else -- our Chief Scientific Officer -- if there's anything else she'd like to add about patterns of immunity we have observed with the platform after the first dose.

Dr. Moore: Thank you, Dr. Miller. I actually would like to send that question over to Dr. Tal Zaks who has more experience with the clinical trials.

Dr. Zaks: Thank you both. So, yeah. I think the salient parts here is that we see binding antibodies come up very quickly. And while everybody focuses on neutralizing antibodies in appropriate lid
cell, I think their sensitivity is lower than looking at the binding assays.

And if you look at binding antibodies, they actually come up within a couple weeks. And so I suspect what happens here is that, as you get the first dose you’re primed, binding antibodies are going to come up. And now you've got a race between is your infection going to in a sense be a boost, because we know this virus takes some time and you're still protected against symptomatic disease.

So I suspect that's the reason for the discrepancy we see between the neutralizing antibodies, that are clearly measurable better after a boost, but the sense that protection may start as early as the first dose. And I think in that regard our results are very concordant with that that were recorded here last week.

So while there is some potentially innate activation, I think the story here really is the SARS-CoV-2, and the quick antibody binding and total
response that you see after the first dose, I'm sure with further -- with the maturation and further increase on that and now you start to measure consistent neutralizing titers.

I will say though, that at the end of the day for me, that first dose efficacy is really supportive evidence overall. But coming back to the fact that what we really studied was a prime-boost, and what we see is clear boosting and a high level of protection across all age groups, and now hopefully that will be durable. And so, I would take the first dose efficacy as supportive evidence, but remind us all that we actually need both doses, as far as we know, to achieve this high level of protection. Thank you.

DR. MONTO: Dr. Sylvester.

DR. SYLVESTER: Thank you, Dr. Monto. I wanted to briefly revisit that blinding versus unblinding issue. As the industry rep, you don't need to convince me that a randomized double-blinded clinical trial is our gold standard.
However, I don't believe this would be the first study that would be the first RCT, that would meet their primary endpoint and vaccinate the placebo group before the protocol-described timeframe ends. I believe that HPV-4 Gardasil and the original pneumococcal conjugate vaccine, Prevnar 7, vaccinated their placebo group after the primary endpoint was met, and the data showed overwhelming evidence of benefit similar to what we're seeing here today.

I don't know Dr. Baden, at Brigham and Women's, but I share his concern about losing a significant portion of his study population without offering the COVID vaccine. And I think his open label continuation seems like a practical solution. Thank you.

**DR. MONTO:** Dr. Meissner.

**DR. MEISSNER:** Thank you, Dr. Monto, and thank you Dr. Miller and others for a fascinating presentation. I have a few questions related to the vaccine that are all related. First of all, why do you
think you were successful with this particular messenger RNA vaccine whereas the previous eight are still in development? Number one.

Number two, when we see adverse reactions in the first 48 to 72 hours, following the administration of a vaccine, do you think that's a reaction to the messenger RNA or more likely to the lipid nanoparticle? And along that line, is there understanding that these are proprietary issues? Can you say anything about differences in the lipid nanoparticle between Moderna's vaccine and the one that we spoke about last week?

And then finally, why did you select a 28-day prime interval between the first and the second dose? Was there a reason for that? Thank you.

MR. KAWCZYNISKI: Jacqueline, did you mute your phone again?

DR. MILLER: I did to not interfere with my colleagues. I apologize. So thank you, Dr. Meissner, for those questions. And what I was saying was, I'm going to start and then I'm going to pass the mic along
to our Chief Medical Officer, Dr. Zaks.

So with respect to our development program for mRNA 1273, and the other development programs we have ongoing. So our company has been in the clinic now for about five years. Most of our programs actually have been in the clinic now for about two years. And the difference between the 1273 program and others, of course, is the unique circumstances in which we find ourselves and the strong medical needs which the vaccine requires.

So we have expedited many elements of the development program, including conducting the three phases of our study staggered, but also much of the conduct has been done in parallel. And that has required an absolute focus and collaboration across multiple groups with their focus as well, on the scientific questions that have been raised throughout the course of development. So for example, what safety data did we need to have available in order to move from one step to the next step?
With respect to your question about the component of the vaccine that is responsible for the reactogenicity, I'll ask Dr. Zaks to join the call now.

**MR. KAWCZYNISKI:** -- sir, you are still muted, sir.

**DR. ZAKS:** I apologize for that. Look, for the vaccine, I think it's also important to note that we're in the midst of a pandemic and it's the paradox event vaccine development for case-driven trial. You know, cases are occurring, unfortunately, and that's why these trials delivered information so quickly.

As it relates to the components -- and this was a point of discussion yesterday with an expert panel convened by the NIH where FDA also attended. I think if you look at the lipid nanoparticle, and you ask yourself about the anaphylaxis, people look at three elements here. There's the PEG component, which is actually not just the PEG, the PEG is connected to a lipid. And in that regard, not all PEGs are the same. And indeed, the PEG and the covalently-attached lipid...
that’s in our vaccine is different than the one in the Pfizer vaccine.

The second potential culprit is the amino lipid, and that's where we and Pfizer used very different -- each are proprietary -- amino lipids. So these are different components. The other components are probably innocuous. Cholesterol, it’s enough in our body, the mRNA itself is unlikely to be the culprit here because it's all naturally in cells.

The final element here is the physical-chemical particle properties, right? Because we know that these particles can actually induce responses in and of themselves due to their physical properties. And in that regard, I would expect that the physical-chemical nature of our particles is actually going to be very different than Pfizer's.

So while we all say, oh there's an LNP here with some lipids and mRNA therefore they must be the same, I actually think that as far as the components likely to be the culprits here, I would not necessarily
assume that. Now, that being said, of course, we're going to be looking very carefully, as has been noted, and continue to collaborate with colleagues to try to understand the mechanism here and make sure that we understand this as the picture evolves.

I think though, the last question you asked was about the 28-day interval. I think that's just basic immunology. I don't think there's a big difference between three weeks and four weeks. In the history of our vaccines, as Dr. Miller alluded to, we've always done a four-week interval between prime-boost. That's sort of based on, you know, immunological first principles of vaccination as we understand it when it starts to be optimal for primates.

But I would note here that the window for the second vaccine actually in the protocol was reasonably wide. It was minus three, plus seven. So, you know, we say four weeks, but there's some spiel there. And I think when we did our analysis, we made sure to include
all that. So I doubt that that is materially different
when the dust settles. Thank you.

DR. MEISSNER: Thank you. And can I ask one
follow up question? So --

DR. MONTO: Uh -- uh --uh --

DR. MEISSNER: No?

DR. MONTO: I'm in the unenviable position of
having about eight hands raised and five minutes to go,
so we're going to have to put that off until later.

DR. MEISSNER: Understood.

DR. MONTO: Mr. Toubman.

MR. TOUBMAN: Yes. Thank you for the
presentation. The data's impressive, but I'm still
nervous about only nine weeks median data. So to try
to put myself ease, a couple questions.

One is, with regard to the severe disease
endpoint. The supposition is that it prevents disease,
it prevents severe disease, but we really need data.
Pfizer did not really have data on that, they have very
few cases. And they were given the opportunity to
provide recent data, they declined.

You have 30 cases in the placebo group and none in the vaccine group, which is great. But is there more recent data? I assume you know how many severe cases there have been since they closed on 11/21. How many cases has that been and has the split reflected the 30 and the zero as before?

My other question is related to the unblinding? This is really important because we don't have enough data and maintaining the placebo-controlled studies is the way to get more data. And your plan is specifically to end that.

We heard a bunch of arguments for that, one of which is you don't want to disadvantage trial participants relative to others. And also that there are supplies that have been set aside that you could use for all the trial participants. You just answered the question you had enough. But I think that's kind of beside the point. The real question is what is the expectation?
And I'd like to ask, if I understand what Dr. Goodman was explaining, he indicated that the participants in your trial were not told that they would jump the line, that they'd be entitled to get the vaccine before others in their same demographic group and their same risk group. And if that's true, they have no expectation of getting it different from anybody else that's in their group.

Is there any other ethical reason why Moderna think its trial participants that got placebo should be getting the vaccine compared to Pfizer, which Pfizer appears has rejected the blinded crossover study? But they have -- according to this letter they just sent out to one of the trial participants in my state -- it's only healthcare workers, 20 percent of our healthcare workers, who are being offered this and the rest are being told it will be at a later date.

I'd like to know if there's an ethical reason, if you haven't told people they're going to all get it, why you're any different than Pfizer and you couldn't
do the same with the 25 percent who are healthcare workers in your trial? And then the rest will be later, and that way you maintain the placebo-controlled study for the remaining 75 percent.

DR. MILLER: Thank you for your questions, Mr. Toubman. Maybe I'll start with the first question about additional data. So as Dr. Fink reviewed in his presentation, we've actually made two submissions to the FDA. So the first was on what was intended to be a first planned interim analysis.

There were so many cases reported in November that actually we achieved our final primary analysis approximately five months earlier than we anticipated. We have continued to collect cases since that submission on December 7th. And we currently have over 450 cases that are actually making their way through the adjudication process.

And you can imagine that our adjudication physicians also have been working extremely hard to keep up with this real tsunami of data that are
becoming available, so I don't have that information available for you today. Do intend, though, to continue to make data cuts and update those efficacy analyses. So that should be in the weeks to come.

Your second question was really about the ethical basis for the proposal to unblind placebo recipients. And I think some of your questions really speak to the interface that Dr. Baden has with the trial participants, so I'm going to turn the floor over to him in a moment. I guess the one thing I would say is, we do have one death that has been reported in our trial, in a case of severe COVID, that occurred in a placebo recipient. And that death weighs very heavily on me.

But I do understand that that death occurred at a time when we did not understand if this vaccine was going to have the efficacy that it does, and we didn't have a clear understanding of what the benefit-risk profile looked like. I do think that with the 450 cases that I just mentioned, additional severe cases
and deaths are a question more of when than a question of if. And I think the knowledge that that may be waiting in some of our trial participant's future weighs heavily on me. But Dr. Baden, will you please also take the floor and discuss the question?

**DR. BADEN:** Yes. Oh, no, thank you, Dr. Toubman, for raising those issues. I think the question is not that they were promised. We should not disadvantage the volunteers, but we have to be practical of where we are.

Unblinding is going on, vaccine is available, the vaccine availability is going to rapidly extend to multiple groups. So it's not as if this will take place over six months to a year; this is going to take place over days to weeks in terms of the extending the vaccine supply to additional groups, such as 1b and 1c. And I think what we need to do is keep the volunteers in the study.

And that keeping it in the study, there's not only one flavor of study. It's not just a double-blind
study. There are other formats of the study that can enable us to learn, particularly to learn about asymptomatic transmission through the serology at the transition point, the nasal swab to look at contagiousness and infectivity. And that if we don't come up with a plan that is easily understood and practical for all of our volunteers, some of whom are very health savvy and some of whom are not, then it will become very confusing and disruptive and corrosive in my view.

And so, I don't think it's an issue of a double-blind study or nothing. There are different formats of an ongoing clinical research trial that leverages or accepts the reality that we are facing, over the next two to six weeks in terms of the transition, as vaccine becomes more available.

MR. TOUBMAN: Thank you.

DR. MONTO: Okay. We're going to have to go on to Dr. Fuller. And let me say --

DR. FULLER: Great.
DR. MONTO: -- in advance that we're going to
eat into our lunch. I'm going to try to break for at
least a short period of time, because we have no breaks
scheduled from now to the end of the meeting. So we
will take a break for a short period of time, maybe for
15 minutes. But since I've got a lot of hands raised,
I'm going to continue to go. Dr. Fuller, please.

DR. FULLER: Thank you, Dr. Monto. And thank
you Dr. Miller and Moderna for your study and what
seems to be a very carefully crafted and executed
study. I have two hopefully quick questions.

One, you mentioned that you will be doing
surveillance on the follow-up in Phase 4, not only to
CDC and FDA, but your own system of real-time global
monitoring of events. The first question is, will that
be done in conjunction also with other vaccines that
may be approved, for example, the one that has already
been approved through Pfizer for EUA?

And then the second question is probably a
little bit more theoretical. You noted that you have
greater pain or third-degree pain for the second injection than the first injection. And I've been wondering about these vaccines that -- especially to the S protein where they boost specific immunity. What happens when people are exposed over and over again to the virus, in a circulating pandemic, when they've been highly boosted to something that binds to say the -- in this case the H2 receptor?

Do you have any idea why there's more pain in the second injection? And do you have any thoughts about this idea of having highly boosted immune systems in the middle of a pandemic, where they're continuously challenged?

DR. MILLER: Yeah. So thanks for both of those questions. And I'm going to go to the second question first, so that afterwards I can turn the floor over to Dr. David Martin who can then speak a bit to the pharmacovigilance plans we have both in conjunction with the safety surveillance systems at FDA and CDC, and also the study we intend to undertake ourselves.
But your question about the reactogenicity observed with the vaccine and could that potentially have to do with vaccinating during a pandemic? So what we've observed, in terms of the vaccine reactogenicity, actually really parallels what we see in terms of the vaccine immunogenicity. So the increase after the second dose really goes along with the increase in neutralizing antibody, that we see in all participants, and the induction of our T-Cell responses.

We did actually have 2.2 percent of the population in the study who did not have a history of COVID-19 disease, but when we tested their baseline swab for RTPCR, and we tested their serology for existing antinucleocapsid antibodies, were found to be baseline seropositive for SARS-CoV-2. And in fact, the observed reactogenicity in that group was lower for both local and general solicited systems.

So we think the vaccine can be safely given to people who have previously been exposed to SARS-CoV-2; and think it's more likely that the increases in
immunogenicity are rather related to the pattern of reactogenicity. And so for the second question, Dr. Martin, would you like to talk about the post-authorization safety study that we are proposing?

**DR. FULLER:** Before you go to the second question, just a quick follow up. So does that mean that when people who are immunized get re-exposed, say during -- you know, over the next three months, to viruses circulating, that the boosted immune systems should not have any systemic effect because of just exposure to the virus? I just don't know the answer to that, and I don't know if anyone does.

**DR. MILLER:** Yes. I think you're right, that -- you bring up a good point. Only 2.2 percent of the population were baseline seropositive in this study. So certainly that is another important reason both to keep the clinical trial ongoing and to follow the patients who might get vaccinated in a cross-over design for their safety events, but also to conduct the post-marketing safety surveillance that we're proposing.
to do. And so perhaps, Dr. Martin, do you want to talk
to the study that we're going to conduct?

DR. MONTO: Briefly, please.

DR. MARTIN: Excuse me?

DR. MONTO: Briefly.


Understood. Thank you, Dr. Fuller, for the question.

So as you were mentioning, visibility for the Pfizer
vaccine as well as the Moderna vaccine. So there are
vaccine-specific administration codes which are brand
specific. And so, the U.S. FDA and CDC surveillance
systems, which have described their activities publicly
in ACIP meetings in the last few weeks, they will be
able to observe both vaccines in a brand-specific
manner and certainly aggregate if they choose to do so.

Moderna, as is customary, will primarily focus
its monitoring on its own product and will obviously
work bilaterally if contacted by the FDA. We've been
notified by the U.S. government that we should expect
communications regarding safety signals from the U.S.
FDA. And so that is customarily how these things are done.

DR. FULLER: Thank you.

DR. MONTO: Okay. Dr. Hildreth, please.

MR. KAWCZYNski: Dr. Hildreth, we're not hearing you. Dr. Hildreth, let's just make sure you're not on mute. There you go. Now we can hear you.

DR. HILDRETH: Can you hear me now? Oh.

Thanks.

MR. KAWCZYNski: Yes.

DR. HILDRETH: First, I was apologizing that we're still not able to get my camera to work. I apologize for that. My question relates to the minorities you've enrolled in the study. My understanding is that many of them, or large numbers of them, enrolled late in the process. And I wonder if you have the same median follow up for those individuals as you have for the study overall?

DR. MILLER: So I don't have the specific data about minorities and the follow up in each of those
groups. It is true that they were enrolled a bit later in the process. And that was really because we invested in working with community leaders to understand what we needed to do in order to make participation in clinical trials something that those communities would -- that are -- again, to Dr. Baden's previous point, building trust with those communities and ensuring that they benefit from the clinical trial in which they have so generously donated their time and their willingness to be examined, is really critical, I think, to encouraging a minority enrollment in future clinical trials.

And we will continue to follow -- as we would propose to transition to an open-label study, we will continue to follow those individuals for further breakthrough cases and for their safety outcomes to generate these very important data.

DR. HILDRETH: Thank you.

DR. MONTO: Dr. Perlman, please.

DR. PERLMAN: Yes. I just have a relatively
quick question. So this vaccine can be kept at room
temperature for some number of hours and at four
degrees for a long time. And since it's an RNA
vaccine, how much degradation of the RNA occurs during
that time? I worry when it goes out to more distant
places that conditions won't be so perfect. So how
long is it really stable?

DR. MILLER: Yeah. So to speak to the
stability studies I am going to as our CMC expert, Dr.
Nedim Altaras, to take that question.

DR. ALTARAS: Hello. Hi. Can you hear me?
Yes? We have started performing our stability studies
very early on in January when we started developing
this vaccine. And we have generated/collection
significant amount of stability since that time, which
we have shared with FDA including our stability at 228
and room temperature. Which basically we provided to
FDA to be able to make the shelf-life claim that we are
making. And FDA, as you have noted in their briefing
document, have agreed with our CMC package that's
suitable for emergency authorization.

DR. PERLMAN: But is there any degradation?

DR. ALTARAS: mRNA have degradation over time at different temperature. And yes, we characterized it and we assured that in terms of the shelf-life, our product remains potent and maintains the quality attributes across all quality attributes to maintain effectiveness. And also during the Phase 3 study, we actually utilized -- we actually put loss in the study representing the quality attributes across the shelf-life of the product.

DR. MONTO: Okay. Final question before we break, from Dr. Rubin, please.

DR. RUBIN: (Audio skip) -- and do you think? And how long does the mRNA stick around for inside the cells?

DR. MILLER: I apologize, Dr. Rubin. I missed the first part of your question. The audio took a moment to come up. Would you mind repeating it, please?
DR. RUBIN: Okay. Sorry. So which cells do you think are important for antigen presentation, and how long does the mRNA last intracellularly?

DR. MILLER: So to answer your question, I'm going to ask Dr. Melissa Moore, our Chief Scientific Officer, to come up in a minute. But the cells that we believe are important for the antigen presentation are the dendritic cells and the subcapsular macrophages. But to give you more detail, Dr. Moore.

DR. MOORE: Thank you for the question. Yes. The main cells, as illustrated on the slide I'm showing here that take up the lipid nanoparticles and express them in the draining lymph nodes, are the monocytes and dendritic cells, also known as antigen-presenting cells. In terms of how long the RNA sticks around, the peak antigen expression is about 48 hours and it's gone by 72 hours. The mRNA is generally gone by around 24 hours. So the protein sticks around longer than the mRNA.

DR. RUBIN: Thank you.
DR. MONTO: Okay. I am going to have to call a mercy rule here for everybody and apologize to the six people with their hands raised right now. Your turn will come later on. We're about 15 minutes late and to allow everybody a little bit of time off, let's start at 2:05. So a 20-minute break right now.

[BREAK]

FDA PRESENTATION AND VOTING QUESTIONS

MR. KAWCZYNski: All right. Welcome back to the Vaccines and Related Biological Products Advisory Committee Meeting. We just came back from our last break, and now we will go into the last portion of today’s agenda. With that, Dr. Monto, go ahead and take it away.

DR. MONTO: I would like to introduce next for the FDA presentation and also a description of the voting questions to Rachel Zhang, who is our next presenter. Dr. Zhang, please.
DR. ZHANG: Hi, good afternoon, everyone. So this is a brief outline of what we will be covering today. First, I will start with an introduction of the Moderna COVID-19 vaccine and a quick run-through of the clinical development program to date. Then, we’ll take a dive into the efficacy and safety data from the phase 3 study. We’ll discuss the pharmacovigilance plan and plans for future studies, and finally we’ll finish with a benefit-risk assessment in context of proposed use under EUA.

So very quick introduction. Moderna COVID-19 vaccine is based on the SARS-CoV-2 spike glycoprotein antigen encoded by RNA, formulated in lipid nanoparticles. It’s given as an intramuscular injection two dose series spaced 28 days apart. Each dose is 100 micrograms. Their proposed indication and usage under EUA is for active immunization, for the prevention of COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

So really quickly, looking at the clinical
development program to date, there are three ongoing studies with the Moderna COVID-19 vaccine. The phase 1 study was co-sponsored by the NIH and is an open-label, dose-ranging study in individuals 18 years of age and older. The phase 2 study is a randomized, placebo-controlled dose confirmation study, also in individuals 18 years of age and older.

Safety and immunogenicity data from phase 1, and additional safety data from phase 2, help inform the dose selection and study design for phase 3. Phase 3, which we will talk a little bit more in depth, is a randomized, placebo-controlled efficacy study in individuals 18 years of age and older.

So looking at the phase 1 study, they enrolled a total of 120 participants in three age cohorts. There were 60 between the ages of 18 and 55, 30 between the ages of 56 and 70, and 30 participants 71 years of age and older. There were four dose levels tested, ranging from 25 micrograms to 250 micrograms. The immunogenicity assessments from the study
showed that two doses induced SARS-CoV-2 binding and neutralizing antibodies, and Th 1-biased CD4 T-cell response was elicited. The safety profile supported further clinical development, and there were no concerning safety findings. As of the time of the EUA request, there has been no serious adverse events reported from the phase 1 study.

The study was staggered in design where the younger cohorts were enrolled earlier than the older cohorts, and some doses were later added on to the study. So there’s a range in follow up duration. At this time, all participants from this study have had at least three months of follow up after dose 2, and a very small number has had up to a six month follow up.

So now looking at the phase 2 study. So in this study there were 600 participants, half between the ages of 18 and 54 and half 55 years of age and older. Subjects were randomized one to one to one, to either the 50-microgram dose, 100 microgram dose, or a placebo. Similar to the phase 1 study, two doses
induced comparable SARS-CoV-2 binding and neutralizing antibodies in both age cohorts. No concerning safety signals were found.

As of the time of the EUA request, there has been three SAEs that were reported in the vaccine group, but none were assessed as related. The immunogenicity and safety data are from the Day 57 data cut, which comes to about one month after dose 2. But SAEs are reported more in real time, so the three SAEs are current as of the beginning of December.

So moving on to the phase 3 study. So in this study 30,351 adults, 18 years of age and older, were randomized one to one and vaccinated with two doses of the vaccine or placebo 28 days apart. Randomization was stratified by age and risk factor for severe COVID-19 into one of these three categories: those 18 to 64 years of age without risk factors; 18 to 64 years of age with risk factors; and individuals 65 years of age or older regardless of risk factors. The protocols specified that the latter two categories should make up
25 to 50 percent of the total study population. And the risk factors for severe COVID-19 specified in the protocol are chronic lung disease, significant cardiac disease, severe obesity, which is BMI 40 or greater, diabetes, liver disease and HIV. All subjects were followed for solicited adverse reactions for seven days after each dose, unsolicited adverse events for 28 days after each dose, and SAEs and medically-attended adverse events for the entire study duration. The planned study duration is two years.

So this is a graphical depiction of the study timeline in terms of scheduled visits and also when the two efficacy analysis timepoints occurred. So starting on the left-hand side, subjects were administered two doses of the vaccine or placebo one month apart. A nasopharyngeal swab for SARS-CoV-2 RTPCR was collected prior to each dose, as well as blood for immunogenicity.

There are further scheduled study visits for
safety and immunogenicity assessments during the follow-
up phase of the study. Throughout the study, subjects
are given weekly e-diary prompts, as well as monthly
safety phone calls. And active surveillance for COVID-
19 symptoms begins after dose one. Looking at the top
of this graph, you'll see the dates of the two analyses
that contributed to the data that we will look at
today.

So this slide just shows the case definitions
used for the efficacy endpoints. So starting from the
left-hand side, the primary efficacy endpoint for
COVID-19 disease, the case definition is positive SARS-
CoV-2 PCR plus at least two of the following systemic
symptoms: fever, chills, myalgia, headache, sore
throat, new olfactory -- sorry, my screen disappeared --
- new olfactory and taste disorders or -- I’ll just
keep going since I have backup slides -- at least one
of the following respiratory signs or symptoms: cough,
shortness of breath or difficulty breathing, or
clinical or radiological evidence of pneumonia. Let me
MR. KAWCZYSKI: Yeah. Just give us a second.

Somebody accidentally hit “stop sharing,” so let me pull it back up. All right? It’ll just take a moment here. Let’s see. I’ve just got to check the names, so it’ll just take a moment. Did you try to hit the arrow accidentally and -- was that it there?

DR. ZHANG: I didn’t touch anything.

MR. KAWCZYSKI: What’s the title of yours?

Oh, okay. Share document. Hold on. We’re just going to take a quick little break. Chad, pull us up on a break just while we pull this up. I want to make sure we get it.

[BREAK]

DR. ZHANG: -- severe systemic illness based on one of the vital signs, respiratory failure or ARDS, shock, significant acute renal, hepatic, or neurologic dysfunction, ICU admission or death.
So this slide shows the primary efficacy endpoint and how it was analyzed. The primary endpoint is, confirmed COVID-19 occurring at least 14 days after dose 2 in participants without evidence of SARS-CoV-2 infection prior to dose 1. And baseline SARS-CoV-2 status is based on RTPCR for SARS-CoV-2 and serology against a nucleocapsid prior to dose 1.

For the primary endpoint, an independent blinded clinical adjudication committee confirmed whether each case met this case definition and should be counted. Vaccine efficacy was defined as the percent reduction, vaccine versus placebo, in the hazard of the primary endpoint, so $V = 1 - \text{hazard ratio}$ from the Cox model. The primary objective would be met if the null hypothesis of $H_0$ vaccine efficacy less than or equal to 30 percent is rejected at any of the interim or primary analyses at the pre-specified O’Brien-Fleming boundary.

There were two protocol specified interim analyses timepoints. The first after 53 cases have
accrued, and the second after 106 cases have accrued. Because of the rapid rise in cases around the time that the first interim analysis was triggered, there were actually 95 cases included in the interim analysis data cut. Similarly, for the primary analysis, which is specified in the protocol to occur at 151 cases, there were actually 195 cases by the time of the data cuts.

These are just two of the key secondary efficacy endpoints included in the study. The first is efficacy against severe disease, using the definition we just looked at a few slides ago, starting 14 days or later after dose 2 in participants without evidence of SARS-CoV-2 infection prior to dose 1. And the second is a less restrictive definition of COVID-19, based on the list of symptoms for COVID-19 by the CDC. And similarly, these are cases confirmed 14 days or later after dose 2, in participants without evidence of SARS-CoV-2 infection prior to dose 1.

Cases of severe COVID-19 are reviewed in real time by the DSMB to monitor to possible signal for
vaccine-enhanced respiratory disease. And a protocol-
specified study stopping rule will be triggered if the
one-sided probability of observing the same or more
extreme case split was less than or equal to 5 percent,
when the true incidence of severe disease was the same
for the vaccine and placebo participants. This was not
triggered for this study. Okay.

Next slide, these are the key analysis
populations defined in the study. So the full analysis
set are all randomized participants who received at
least one dose of vaccine or placebo. Participants are
analyzed according to the group to which they were
randomized. The modified intent to treat set are all
participants in the full analysis set, who had no
evidence of prior SARS-CoV-2 infection day one before
the first dose.

The per protocol set are all participants in
the modified intent to treat set, who received the
planned doses per schedule and have no major protocol
deviations. The safety set are all randomized
participants who received at least one dose -- and sorry for the typo here. As opposed to the full analysis set, in the safety set they are analyzed according to the treatment they actually received. So this slide will hopefully make it easier to see the difference in median follow-up duration for the two different analysis that we’re going to look at today. So on November 30, Moderna submitted data from their interim analysis to support an EUA, and as you can see in the orange bars, the median follow-up for safety and efficacy in these subjects at the time of the interim analysis was seven weeks after dose 2. To align with the expectation for a minimum of two months of follow up, as outlined in FDA’s guidance, Moderna later submitted on December 7 additional data from the scheduled final analysis as an amendment to the EUA. As you can see in the blue bars, the median follow up for safety and efficacy at the time of the final analysis was around nine weeks after dose two. So the majority of the slides that I will
present today will show data from the interim analysis unless it’s otherwise specified as the final analysis data. However, I just want to note that we have independently verified the vast majority of the analysis from the final analysis, and this includes the primary endpoint, the associated subgroup analyses with the primary endpoint, the key secondary endpoints, and the solicited and unsolicited safety data, including serious adverse events. We have not identified any notable differences in terms of efficacy or safety profile with these additional two weeks of data, so these data did not alter the conclusions that we had already arrived at after thorough review of the interim analysis data.

So moving on into the efficacy data, so this table shows the demographic characteristics of the study population, and you can see that it was very similar among the vaccine and placebo participants. The median age was 53 with a range of 18 to 95. Around 25 percent of participants were 65 years of age and
older. Looking at race and ethnicity, we have 9.7 percent of subjects self-identified as African-American, 4.7 percent Asian, 0.8 percent American Indian or Alaska Native, 0.2 percent Native Hawaiian or Pacific Islander, 2.1 percent other, and 20 percent of subjects self-identified as Hispanic or Latino. Around 25 percent of the study participants were healthcare workers, and based on protocol defined risk factors for severe COVID-19, around 22 percent of study participants had at least one high-risk condition present.

So this is a subject disposition table, and looking at this you can see around 8 percent of subjects were excluded from the per protocol set, which is the set used for the primary efficacy analysis. And the primary reason was the subject being positive or having an unknown baseline SARS-CoV-2 status prior to dose 1. Around 95 percent of the subjects completed two doses in the per protocol set, and discontinuation from the study was rare, with only 0.2 percent from
either group.

So now here is the primary efficacy endpoint at the scheduled final analysis, so if we can look at the top line, in all subjects there were 11 cases of COVID-19 in the vaccine group compared to 185 in the placebo group, with a vaccine efficacy of 94.1 and a 95 percent confidence interval of 89.3 to 96.8. Dividing that up into age subgroups, in the 18 to less than 65 years age group the vaccine efficacy point estimate was 95.6, so very similar to the efficacy in the overall population. In the 65 years and older age group, the vaccine efficacy point estimate was slightly lower at 86.4 percent. However, the number of cases are small, and the confidence intervals overlap with those in the younger age cohort and the overall study population.

This is a subgroup analysis of the primary efficacy endpoint broken down into further age categories, stratification categories, and sex. And you can see that vaccine efficacy in each subgroup was comparable to the over study population. And again,
going through these next few slides, shown here is the interim analysis, but we have verified the final analysis for these subgroups. And there’s no notable difference.

This is the subgroup analysis of the primary efficacy endpoint by race and ethnicity. As you can see, efficacy was uniformly high across the groups. However, I do want to point out that for many of the subgroups the sample size and the case numbers are small, and that limits the interpretability of the individual efficacy results.

This is a subgroup analysis of the primary efficacy endpoint by the protocol defined risk factor for severe COVID-19 and also includes at the bottom a post-hoc analysis of obesity, defined as BMI greater than 30. Again, as you can see, efficacy across the board is consistent with what was seen at primary endpoint, but for some of these groups, it is, again, limited by the small number of cases in the population.

So this is a subgroup analysis of the primary
efficacy endpoint by baseline SARS-CoV-2 status, and just as a reminder, that is based on RTPCR and serology against a nucleocapsid protein prior to dose 1. Just over 2 percent of the study subjects were positive at baseline, so you can see that there is just one single case in the seropositive. So there’s not really any sufficient data to make any conclusions on vaccine efficacy in participants with a prior history of SARS-CoV-2 infection.

This is the secondary efficacy analysis of severe COVID-19 at the scheduled final analysis, so looking at all subjects, there were 30 cases in the placebo group. And nine of these cases resulted in hospitalization, and one resulted in death. In the vaccine group, we do note that there was one severe case in a vaccine recipient which occurred two months after dose 2, requiring hospitalization, but had not been adjudicated by the time of the data cutoff.

This is the cumulative incidence curve of COVID-19, starting after randomization in the modified
intent to treat set, and the arrow’s showing where the vaccine doses were given. And as you can see, the curve starts to diverge a little bit after the two weeks mark, and the divergence becomes more prominent as time goes on and more cases start accumulating in the placebo group.

This is a post-hoc analysis of COVID-19 cases from time of randomization in the full analysis set, so that means this includes all participants who have received at least one dose of either placebo or vaccine. And it’s regardless of baseline SARS-CoV-2 status. So just looking at the second line, efficacy any time after dose 1 to before dose 2 was around 69 percent, so this could suggest some protection after the first dose. But data’s limited by the very short follow up, so around 28 days, as the majority of the study subjects received a second dose. Okay.

Now moving on into the safety data, this again is a graphical depiction of the scheduled safety visits and safety calls throughout the study. Just as a
reminder, all solicited adverse events are collected from all study subjects via an e-diary for seven days after each dose. Unsolicited adverse events are collected for 28 days after each dose, and serious adverse events and medically attended adverse events are captured throughout the entire study.

This is a subject disposition table, and you can see a vast majority of subjects completed two doses and very small percentage discontinued the study. And it was similar between the vaccine and placebo groups.

Okay. The next few tables are going to show the solicited local and systemic reactions, but, again, before we dive into it, I just want to reiterate that although the data shown are from the interim analysis data, we have verified the data from the final analysis. And there was no notable difference compared to the interim analysis data shown here.

So looking at the solicited local reactions after dose 1, you can see the most commonly reported local reaction was pain. Grade 3 events were rare
after the first dose, and something that you see
through the next few tables is that there is a lower
rate of solicited reactions in the elderly cohort
compared to the younger cohort. This is looking at
solicited local reactions after dose 2. It is slightly
higher compared to after dose 1. Grade 3 events are
still pretty low.

Now switching to systemic reaction after dose
1, similar to the local reaction, there’s a lower rate
in the elderly compared to the younger adults. And
after dose 1, grade 3 or 4 events were rare. And
finally looking at solicited systemic reactions after
dose 2, you can see there is a higher rate after dose 2
compared to dose 1, including a higher rate of grade 3
events. So for example, fatigue, myalgia is around 10
percent grade 3. Overall, based on review of these
last four slides, there were no serious safety concerns
based on the data. Okay.

Shown here is an overview of solicited safety
by baseline SARS-CoV-2 status. The rates of solicited
adverse reactions were comparable or sometimes slightly lower in participants with baseline positive SARS-CoV-2 status. But again, this group is much smaller in size compared to participants with negative SARS-CoV-2 status at baseline.

This table shows unsolicited adverse events rates overall and then further broken down into which of those are related, which are considered serious, and medically related adverse events and then also broken down by baseline serostatus. So again, the rates of these events are comparable or a little bit lower in those who are baseline SARS-CoV-2 positive compared to those who are negative at baseline, but, again, that subgroup population is small. Unsolicited adverse events in general was comparable between the vaccine group and the placebo group.

So FDA conducted standard MedDRA queries, SMQs, using FDA developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the data cutoff. The SMQs
were conducted on adverse events preferred terms that could represent various conditions, including, but not limited to, allergic, neurologic, inflammatory, and autoimmune disorders. Here, we just highlight the unsolicited adverse events which had a higher frequency in the vaccine group versus placebo.

So starting with hypersensitivity related events, there was 1.5 percent in the vaccine group versus 1.1 percent in the placebo group. And the most frequently reported AEs in the hypersensitivity SMQs were injection site rash, injection site urticaria, and maculopapular rash. This we thought had a possible relationship to the vaccination. And then also of note, no anaphylactic or sever hypersensitivity reactions with close temporal relation to the vaccine were noted.

Lymphadenopathy-related events -- that’s outside of the solicited period -- was noted in 1.1 percent of vaccine recipients and 0.6 percent of placebo recipients. The most frequently reported
lymphadenopathy SMQs were injection site
lymphadenopathy, lymph node pain, and lymphadenitis.
Again, we thought this had a plausible relationship to
vaccination. We also noted delayed localized injection
site reactions with onset after seven days, seen mostly
after dose 1. And this was noted in 1.4 percent in the
vaccine group versus 0.4 percent in the placebo group.

There was a numerical imbalance in Bell’s
palsy cases with three cases in the vaccine group and
one case in the placebo group. The case in the placebo
group occurred 17 days after dose 1. The three cases
in the vaccine group occurred 22, 28, and 32 days after
dose 2. The observed rate was consistent with the
background rate in the general population. And there’s
no clear basis upon which to conclude a causal
relationship at this time.

Moving on to serious adverse events and
deaths, as of December 3, there were 13 total deaths
reported in the study, with six in the vaccine group
and seven in the placebo group. None of these deaths
were assessed as related. Really quickly, in the vaccine group the first three participants listed all had underlying cardiac disease. The first subject died of cardiac arrest 21 days after dose 1. The 77-year-old participant died of myocardial infarction 45 days after dose 2. The 70-year-old subject was found deceased at home 57 days after dose 2.

The next participant was a 56-year-old subject with hypertension and chronic back pain being treated with opiate pain medication who was found deceased at home 37 days after dose 1, and the official cause of death was head trauma. Then, we have a 72-year-old participant with Crohn’s disease and short bowel who was hospitalized 40 days post-dose 2 due to thrombocytopenia and acute kidney failure and then later developed complications during the hospital stay, including a perforated ulcer that resulted in multi-organ failure and death 59 days after dose 2. And last, we have a 62-year-old participant who died of suicide 21 days after dose 1.
There were three SAEs thought related by the FDA. One is a 65-year-old participant with a history of severe headache and nausea requiring hospitalization who developed intractable nausea/vomiting requiring hospitalization one day post dose 2. And there were two subjects who reported facial swelling one day and two days post dose 2. Both of these subjects had a prior history of dermal filler cosmetic injections in the cheeks. For one subject, it was about two weeks before vaccination, and for the other subject, it was about six months before vaccination.

Also related, but there was one subject who had lip angioedema about two days after vaccination, and that subject also had prior dermal filler injection in the lip. Interestingly, that subject reported a similar reaction after a previous influenza vaccine. I do want to point out that for these three subjects that I just mentioned -- so the two with the facial swelling and the one with the lip swelling -- the swelling was only localized. There were no systemic symptoms.
Women were screened for pregnancy prior to each vaccination, and a positive test resulted in exclusion or discontinuation from vaccination. As of December 2, there were 13 pregnancy in the study, six in the vaccine group and seven in the placebo group. Vaccination occurred prior to last menstrual period in two vaccine recipients and three placebo recipients. Vaccination occurred within 30 days after LMP in two vaccine recipients and three placebo recipients, and vaccination occurred greater than 30 days after LMP in one vaccine recipient and one placebo recipient. The LMP is not known in one vaccine recipient. In terms of outcomes, there’s one case of spontaneous abortion and one elective abortion in the placebo group. Otherwise, all the other pregnancies are ongoing, and the outcomes are not known at this time.

So in summary, for the efficacy, the totality of the clinical data submitted with the EUA request meets the expectations for duration of follow up. In
the scheduled final analysis, vaccine efficacy 14 days
or later post dose 2 was 94.1 percent with a confidence
interval of 89.3 to 96.8 in participants without prior
evidence of SARS-CoV-2 infection. Efficacy outcomes
were consistent, greater than 93 percent, across
demographic subgroups. In the scheduled final
analysis, there were 30 sever cases of COVID-19 in the
placebo group and one still unadjudicated case in the
vaccine group. The data suggest the potential efficacy
following a single dose, but interpretation is limited
because almost all participants received a second dose.
As far as for safety, the totality of the
clinical data submitted with the EUA request meets the
expectations for duration of follow up in greater than
30,000 participants. Reactogenicity was generally more
frequent after dose 2 in all age groups, mostly mild to
moderate and less frequent and severe in adults 65
years of age or older. There were no safety concerns
identified in subgroup analyses by age, sex, race,
ethnicity, health risk for severe COVID-19 or prior
SARS-CoV-2 infection. Lymphadenopathy reported as solicited and unsolicited adverse events were more frequent in the vaccine group compared to placebo. A delayed localized injection site reaction with onset after seven days was more frequent in the vaccine group compared to the placebo and mostly seen after dose 1. Hypersensitivity related events were more frequent in the vaccine group compared with placebo, but no anaphylactic or severe hypersensitivity reactions with temporal relation to vaccination was noted. As of the scheduled final analysis, three cases of Bell’s palsy were reported in vaccine recipients and one in placebo recipients. Although there’s no clear basis upon which to conclude a causal relationship at this time, FDA recommends further surveillance if vaccine is authorized for widespread use.

Moving on to the pharmacovigilance plan, Moderna submitted a pharmacovigilance plan to monitor safety concerns that could be associated with the
Moderna COVID-19 vaccine. The sponsor identified vaccine associated enhanced disease, including vaccine associated enhanced respiratory disease and anaphylactic reactions, including anaphylaxis, as the important potential risks. Use in pregnant and breastfeeding women, use in pediatric population, long-term safety and long-term effectiveness, immunogenicity in subjects with immunosuppression, and concomitant administration with non-COVID vaccines are areas the sponsor identified as missing information.

Pharmacovigilance activities, including adverse events reporting -- adverse events reporting under EUA, may come from vaccine recipients, vaccination providers, or the sponsor. First, the vaccine recipients will be notified that an adverse event can be reported to VAERS in the fact sheets for recipients and caregivers. Another source of adverse event reports from recipients is the V-Safe program, which is a smartphone-based program that uses text messaging from web surveys from the CDC to check in
with vaccine recipients for health problems after vaccination.

Reports from vaccine recipients are voluntary. Adverse events reported by vaccine providers and the sponsor is mandatory. Both the sponsor and vaccine providers administering the Moderna COVID-19 vaccine must report to VAERS the following information associated with the vaccine: vaccine administration errors, whether or not associated with an adverse event; serious adverse events irrespective of attribution to vaccination; cases of multisystem inflammatory syndrome in 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 periodic safety reports at monthly intervals for FDA review. Each periodic safety report is required to contain a narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age group,
special populations -- such as pregnant women -- and adverse events of special interest, newly identified safety concerns in this interval and actions taken since the last report because of adverse experiences. Both FDA and CDC will take a collaborative and complementary approach to reviewing adverse events.

FDA will individually review all serious adverse events on a daily basis. FDA will also examine other sources for adverse events, such as the literature, and will perform datamining 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 sponsor provided a description of studies they are currently planning on conducting. The studies will include completion of long-term follow up from ongoing clinical trials, as well as the following two planned safety surveillance studies. The pregnancy cohort, the sponsor plans to establish a passive
pregnancy registry to monitor vaccination during pregnancy with populations expected to receive the vaccine under an EUA and to submit a protocol for FDA review and approval. Active follow up for safety, this study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives: estimation of background rates of 23 pre-specified adverse events of special interest, descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. FDA will provide feedback on these studies after further review of protocols once submitted by the sponsor.

Proposed revisions to the ongoing phase 3 study if an EUA is issued is still in discussion. We have not yet received a revised protocol for review. In general, Moderna’s proposing that there will be no changes for participants who choose to remain blinded,
but for participants who chose to be unblinded, they will proactively reconsent and offer vaccine for those in the placebo group. Regardless of whether the participant remains blinded or unblinded or which treatment they receive, all participants will continue to be followed for two years.

Finally, we will now go into the benefit-risk assessment. So the known benefits of the vaccine:
reduced risk of confirmed COVID-19 at least 14 days after completing a two-dose vaccination regime in individuals without prior history of SARS-CoV-2 infection; reduced risk of confirmed severe COVID-19 at least 14 days after completing a two-dose vaccination regimen in individuals without prior history of SARS-CoV-2 infection. And in the subgroups, efficacy findings are consistent across subgroups by age, race, ethnicity, and comorbidities.

The known risks, so local and systemic adverse reactions are reported at a higher rate after a second dose and a higher rate in younger adults compared to
older participants. There were three SAEs we thought related to vaccination, and they were all temporarily associated and biologically plausible. And this includes the one subject with a history of severe nausea that had the intractable nausea and vomiting and then the two cases of facial swelling in subjects that had a prior dermal filler injection.

Serious hypersensitivity reactions have not been reported in this study but have been reported in clinical experience with Pfizer mRNA vaccine. No specific safety concerns were identified in analyses of subgroups, including prior SARS-CoV-2 infection. The limitations of our risk assessment include the short follow up duration and the fact that pregnant women were excluded.

Here, just to remind everyone the question that we would like the Committee to discuss, in considering Moderna’s plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and
effectiveness to support licensure that should be accrued in ongoing clinical trials with Moderna COVID-19 vaccine, other studies, such as additional clinical trials or observational studies with the Moderna COVID-19 vaccine. And here is the question for vote. Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older? And this is the end of my presentation. I welcome any questions.

COMMITTEE DISCUSSION AND VOTING

DR. MONTO: Thank you, Dr. Zhang, for not only being succinct and comprehensive but also keeping us to time. What I propose is that first we entertain questions for Dr. Zhang on her presentation and then go into a broader questioning of both Dr. Zhang and the sponsor about issues related specifically to the vaccines and the vaccine trials as has been reported.
We should reserve the discussion about the unblinding issues to the later comprehensive discussion that the Committee has, which will go on for a couple of hours, including the voting discussion.

So first, let’s ask questions if you have them for Dr. Zhang, and then we can have broader discussion. And I’ve alerted the sponsor to be ready for these questions. And when we get into the Committee discussion about unblinding, we really need to focus on that issue. We got a hybrid discussion last week for those who were on with the Committee, and I think we want to avoid that and focus on the FDA discussion points. So Dr. Offit, please.

DR. OFFIT: Thank you, Dr. Zhang, for a clear presentation. I just want to follow up on something that both Dr. Cohn and Dr. Gans brought up earlier, which is just briefly this issue of Bell’s palsy. And I understand that we’re looking through -- there’s the tyranny of small numbers derived from the large database, and you can’t determine causality from such
small numbers. And I’m really glad that you’re doing
follow up, but I don’t quite see how we’re comfortable
that what we’re calling -- what we’re seeing with both
the Pfizer trial and Moderna trial are background
rates.

If you look at the Pfizer trial, it was four
cases of Bell’s palsy in a group of 22,000 vaccinees
per three months, which works out to about eight cases
per 10,000 per year. If you look at the Moderna trial,
it’s three cases per 15,000 per few months, which also
works out to about eight cases per 10,000 per year. If
you look at the one placebo case and if you add the two
placebo groups -- it’s roughly 37,000 over a few months
-- that works out to about 1.2 cases per 10,000 per
year, which at least what I had read was roughly the
background rate.

That in combination with the fact that SARS-
CoV-2 has been reported to be a cause of Bell’s palsy
in a handful of people and presenting actually -- the
first presentation being Bell’s palsy and then found to
have SARS-CoV-2 offers at least some biological plausibility. And in fact, it may be true that SARS-CoV-2 is a more common cause of Bell’s palsy than this vaccination, and we’ll find this all out in follow up. But I’m just not quite sure how we are so comfortable that this was a background rate. I guess that’s my question. Thank you.

DR. ZHANG: Sorry, I just had to find the unmute button. Yes, this is something we’re also looking into and thinking a lot about. Just based on each of these individual studies, we’re looking at the cases -- there is still no clear basis upon which to conclude a causal relationship, but we definitely see your point with the two studies combined -- the numbers. And it’s something that we are looking into and thinking much about.

DR. OFFIT: Thank you.

DR. MONTO: All right. Thank you. Dr. Wharton, please.

DR. WHARTON: Thanks. I’m interested in these
three cases of facial swelling associated with the
prior injection of the dermal fillers. How long did
those swelling reactions take, and should this product
be authorized, will this information be included in the
information for healthcare providers?

DR. ZHANG: Okay. I can just give you a
little bit more information on those cases. Again, all
three of those cases that I mentioned were just
localized, like swelling in the cheeks or swelling in
the lips, and they resolve with either antihistamines
or a steroid course. And again, no systemic reactions
were noted, and it was really interesting that one
participant who reported a similar reaction after
previous vaccine.

And we did a literature search, and it seems
that this is something that has been reported -- that
with these dermal filler injections there could be some
interaction with the immune response after a natural
infection, such as, like, an influenza-like illness,
with these dermal fillers that create this temporary
swelling that usually resolves pretty quickly with steroids or by itself. So we are planning to note this in the prescribing information.

**DR. MONTO:** Thank you. Dr. Gans?

**DR. GANS:** Thank you. Thank you for that. I just had one question about a clarification. You had noted some of the regulatory events that will happen in terms of adverse events, and you listed it only under EUA, which obviously is what we’re considering now. And I just wanted to clarify that those functions will continue as we move out of an EUA into maybe a BLA or other forms in which we should still be looking at adverse events as this vaccine is rolled out. So I just wanted to make sure that it wasn’t so specific to just under an EUA.

**DR. ZHANG:** Yes, so if you remember that really busy slide with a lot of boxes and arrows -- so the surveillance and follow up for an EUA is not any less demanding or more demanding than a regular BLA, so all of those will continue.
DR. GANS: Thank you.

DR. MONTO: Dr. Sawyer?

DR. SAWYER: Thank you. My question relates to the anaphylaxis story, and you described an imbalance in hypersensitivity reactions between the vaccine and placebo groups but that there was no cases of anaphylaxis. I wonder if you can characterize for us what those hypersensitivity events are because I wonder if some of the media reports are reflecting hypersensitivity reactions that aren’t truly anaphylaxis, things like simple hives -- at least until those cases get fully adjudicated.

DR. ZHANG: Sure. Thank you for that question. So like I mentioned, when we searched by the SMQs, the most common preferred terms event that we found under the hypersensitivity related events were injection site urticaria, injection site rash or rash in general or hives or itching. So nothing that really are close even to anaphylaxis.

DR. SAWYER: Thank you.
DR. MONTO: Dr. Neaton?

DR. NEATON: Thank you. Thanks for the presentation. I wondered a couple things on the safety. I noticed for the safety kind of cohort that was looked at there was an excess of withdraws of consents in the placebo group. Did you notice that, and was there anything -- reasons for those withdraws that could make you question the blinding or whether due to adverse events? There was quite an excess.

DR. ZHANG: Yeah. It was a little bit imbalanced in terms of withdraw by subject, but it wasn’t due to adverse events or physician decision due to any medical conditions or anything. Overall, the numbers are still very small. There’s a difference of maybe, like, 60 subjects between the vaccine and placebo group, so looking at the overall safety set, it doesn’t really make any impact.

DR. NEATON: More the difference I was thinking about -- it’s like three or four standard error difference, which seems potentially not due to
chance. Okay. My other question was is in the FDA book you provided more information about the duration of some of the solicited symptoms, and I noticed that, for example, a lot of the symptoms -- if you just take myalgia as an example, there’s a pretty striking difference if you look at solicited symptoms, but the difference is very, very small with unsolicited symptoms. And is that, do you think, primarily attributable to the timing of when those measurements were made?

DR. ZHANG: Yes, correct. The solicited symptoms were collected within the first seven days after vaccination. That’s when we expect most of these symptoms like myalgia, fatigue, and things like that to occur.

DR. NEATON: Is there any medication provided to patients or recommendations for medications to prevent kind of some of the symptoms that were recorded?

DR. ZHANG: I don’t have that data offhand,
but there is -- a use of antipruritics was also collected in the e-diary.

DR. NEATON: Thank you. That’s all for now.

DR. MONTO: Thank you. Dr. Kurilla.

DR. KURILLA: Thank you. Yes, this is about the potential for correlates of protection out of this trial. There was no immunogenicity data that was presented as part of the phase 3. But looking at the phase 1 immunogenicity, particularly in the elderly population in the two-and-a-half-month period, there was rather substantial drop-offs in both the total ELISA as well as the neutralization titers that were measured. And I’m wondering, from your presentation, it looks like there was a blood draw at day 57 but not another one until 209, and I’m wondering if there’s just an adequate measurement of immunogenicity in that phase 3 to try to derive potential correlates of protection.

DR. ZHANG: Maybe I’ll ask Moderna to address how they’re planning to assess correlate of protection
in their studies.

**DR. MILLER:** Sure. Happy to do so. So the correlate of protection, as you noted, are the immunogenicity assays that were not yet available at the time of submission of the EUA. We’re anticipating that the immunogenicity analyses should be available in the coming months. And so trial actually routinely got blood samples at various time points, so pre-dose 1; pre-dose 2; at day 57, which is one-month post-dose 2; and then at three, months, six months, and 12 months afterwards. And the idea would be that we would first present the immunogenicity analyses, and then once we have sufficient break through cases to be able to perform the zero correlate analysis, that will be done as well. We’re actually working in collaboration with the NIH, so Dr. Follmann and Dr. Peter Gilbert, to pull together this analysis. And it actually will be done with NIH assays in order to be able to look at consistency across other products.

**DR. MONTO:** Dr. Fuller?
DR. FULLER: Yes, thank you. So Dr. Zhang, there’s some side effects which are expected with most vaccines, and they’re just part of what happens. Especially in this time when COVID is such a major issue, what is FDA or CDC or Moderna -- perhaps Moderna has a plan for informing people of what to expect. In other words, we can handle things if we know that this is part of what’s expected and it’s only going to be a few days and we have somewhere to report it to if we think otherwise. So I don’t remember the plan for how people will be informed of what the side effects may be as they go to take this vaccine. Can you help remind me, please?

DR. ZHANG: Well, I do know that the side effects are going to be described in detail in the fact sheets for providers, as well as for the recipients. I’ll open up for other people to chime in the other things.

DR. FULLER: So I guess I’m asking if there’s going to be some sort of campaign to make sure that
people -- you know, we all get fact sheets with our medicines or our vaccines or whatever, and we read them sometimes. And sometimes we don’t. And you could say that’s on the person who’s taking it, but for something like this it would be really helpful and build trust if there’s a major effort to say “This is what you should expect. These have been seen often, and these have not been seen.” That would, I think, give people a lot more confidence.

**DR. FINK:** Hi. So as you’ve heard, we have an intensive safety surveillance system stood up for distribution of vaccine under EUA. We’ll be monitoring the system closely. If we detect any signals, we will investigate those rapidly. And if we conclude that there is a need to inform vaccine providers or recipients or the general public about a risk that has not been previously appreciated, we will do so in revisions to labelling or sooner through safety alerts if we determine that that’s warranted.

**DR. MONTO:** Thank you. Dr. Hildreth? Dr.
Hildreth?

**DR. HILDRETH:** Did you call my name? I’m sorry.

**DR. MONTO:** I did. You had your hand raised.

**DR. HILDRETH:** Yes, sir. I did. My question relates to the fact that for every diagnosed case of COVID-19 there are probable several others that go undiagnosed. And I’m wondering if by giving the persons who’ve already been infected a single injection of the vaccine could that serve as a boost and achieve the same goal as giving two injections of the vaccine? In other words, infection serves as the prime and one vaccination will serve as the boost. Is that something that Moderna or FDA has considered as a possibility, just out of curiosity?

**DR. ZHANG:** I’ll defer this to Moderna. This was not in the scope of the data or the study design.

**DR. HILDRETH:** Okay.

**DR. MILLER:** So just to make sure, Dr. Hildreth, I understood your question, are you asking
about the interchangeability of our vaccine with the other mRNA vaccine -- whether you could get a mixed schedule of both?

**DR. HILDRETH:** No, I’m referring to the fact that we now know that there are probably tens of millions of Americans who’ve already been infected by the SARS-CoV-2, and we know they can get reinfected. We also know that all of them make an antibody response through the virus, but it appears not to be protective against -- they can get reinfected. What I’m asking is, if you took the ones who’ve already been infected and gave them an injection of your vaccine, could that possibly serve as a boost whereas the infection itself served as the prime?

**DR. MILLER:** Okay. Thank you for that clarification. So I think it’s something that we may be able to tease out a bit in our booster study. I mean, again, we had only 2.2 percent of the study population that indicated that they were previously SARS-CoV-2 positive.
DR. HILDRETH: Okay.

DR. MILLER: We are intending to evaluate booster doses, and as we review the immunogenesis, that is certainly something we can look at. And once the immunogenicity data are available, we’ll be able to see what the initial vaccination looked like in the mRNA 1273 group. So we don’t have data unfortunately to share with you today, but we are anticipating those data in the coming weeks and months.

DR. HILDRETH: Thank you.

DR. MONTO: Thank you. And Dr. Miller, don’t go away because we’re expanding the discussion right now. Dr. Meissner has been waiting to ask some questions of you.

DR. MEISSNER: Thank you. One question I’d like to ask is about the forest plots that are on Figure 7 and 8, and I realize you probably don’t have this right in front of you. But my question is there were approximately 9,000 white subjects in the placebo arm and 5,000 from communities of color. But the rates
of infection were 16 per 1,000 versus eight per 1,000 in the communities of color, that is they were lower. And usually, we think of COVID-19 causing more disease in the community of color. Is there a ready explanation for that? Perhaps it’s the small numbers. Do you think that was truly representative of minority groups?

DR. MILLER: So thank you for that question. I’m attempting to pull up that forest plot slide now so that -- just to reorient everyone to the discussion we’re having. So to your question about the small numbers, it is true that enrollment of minorities in the trial was a priority for us. We received lots of help and advice from our collaborators and from thought leaders in those communities. Nonetheless, the study was not designed to look at individual efficacy estimates in various demographic groups. And so indeed, the numbers in each specific group are quite small. The study was actually powered only for the symptomatic COVID-19 disease.
Hopefully, we’ll have some refinement of those numbers. Regardless of what happens with the evolution of the clinical trial, we will continue to follow the participants who have been vaccinated with vaccine, placebo, or have been crossed over for COVID-19 disease using the same methods that we’ve used. I and think that the trial has assessed the cases of COVID-19 that occur (audio skipped) our overall attack rate was 56 approximately per 1,000 person years, which is close to reported rates in the literature. So hopefully we’ll be able to further add to those numbers and get some more refinement on them.

DR. MEISSNER: Thank you. I’d like to ask secondly a question in regard to sterilizing immunity. I think your preliminary figures are very promising -- that the vaccine may reduce infectious virus and the risk of transmission of fully replication competent virus. Has there been any effort to look at antibodies in respiratory secretions from the upper respiratory tract or the lower respiratory tract because I -- if
this is in fact true, I guess it means the intramuscular injection stimulated sufficient circulating IgG so that it gravitated out into the mucus membranes of the respiratory tract? Is that reasonable?

DR. MILLER: So I think you’re correct that it’s certainly reasonable to expect that IgG is playing an important role in what we’re seeing from an efficacy perspective. I don’t have data on the IgA, but what we will have to hopefully be able to help us better understand viral shedding and burden of infection are the viral shedding samples that were taken from cases confirmed by RTPCR to be SARS-CoV-2. So those subjects submitted a sample every few days over the month of their convalescence. And ultimately, we’ll take those results and compare in the breakthrough case -- the placebo cases what viral shedding --

DR. MONTO: All right. And Dr. Meissner, that’s something you may want to bring up in our discussion about other studies the sponsor might be
asked to do. Dr. Pergam?

DR. PERGAM: Thanks for a great presentation, guys. My question is specifically around additional data transparency. A lot of what you’re talking about here is things that are coming down the line, and I’m just trying to figure out additional shedding data, additional follow ups that you’re talking about. Moderna has been really transparent with data so far. I’m curious about what the FDA’s approach is going to be in presenting this additional data to the public and to other community members as this moves forward.

DR. MILLER: Apologies, Dr. Pergam. I think that was a question for Dr. Zhang, but I just want to be sure I understood that correctly.

DR. MONTO: Dr. Fink?

DR. FINK: Yes, so we will continue to update the prescribing information and fact sheets as appropriate as we get new information. And if we determine that information is necessary to inform vaccine providers and recipients about the benefits and
risks of the vaccine, of course we will include as part of our review process for any licensure application a transparent review of the data to support that application as well.

**DR. MONTO:** Thank you. Dr. Perlman?

**DR. PERLMAN:** Yes, so I just had a question about the vaccine adverse events, the respiratory disease and the general systemic problems that occur after vaccination. It’s mentioned in the protocol, but there aren’t really very many details of what’s going to actually be looked at. And the fact it’s so efficacious may make this -- makes it less of an issue, but still what’s the exact plan for measuring adverse events after vaccination -- the respiratory disease and the other (audio fade out)?

**DR. MILLER:** Sure. I can take that one and speak to the various ways in which we’re measuring safety in the protocol. So after vaccination, subjects had an electronic diary on which they recorded solicited local symptoms, so the injection site
reactions and then solicited systemic symptoms, like fatigue, headache, myalgia. After seven days, the e-diary, as well as safety phone calls from the site, prompted subjects to respond back about unsolicited adverse events. So these were any adverse events that may have happened to them, and we followed those 28 days after each vaccination.

Then, for some specific categories of adverse events, including medically attended AEs, as well as serious adverse events, we are going to continue with the safety phone calls throughout the duration of study for the subjects and capture that information. And so that’s really the framework in which the respiratory illnesses you’re speaking about will be captured. Then as part of the efficacy surveillance, there’s also the surveillance for COVID-19 disease, and for those subjects who are not COVID-19 positive or SARS-CoV-2 virus positive, we’ll also be looking at a respiratory panel of viruses to try to understand that respiratory disease. And again, some of these endpoints are not
yet available to be reported out, but we intended to continue that surveillance throughout the study.

DR. PERLMAN: Yes. I guess I really meant vaccine enhanced --

DR. MONTO: Okay. Thank you. We’re going to have two more questions, and then we’re going to be shifting and going to a discussion among the Committee of FDA questions. So Dr. Chatterjee next.

DR. CHATTERJEE: Yes, thank you, Dr. Monto. I have two questions, Dr. Miller. The first one is with regard to the nanoparticles. I think we heard today about the rate of decay of the mRNA and the protein that it codes for, but what about the nanoparticles? How long do they hang around?

DR. MILLER: Yes. So the nanoparticles have been evaluated in biodistribution studies, and they hang around for approximately 48 hours.

DR. CHATTERJEE: I see. And then the follow up question to that is, is there a theoretical possibility that the body will mount an immune response
to the nanoparticles, the lipid itself? And if that
happens, would it then preclude the use of these
nanoparticles for any future vaccines that are
developed in the same manner?

DR. MILLER: So to answer that question, I’m
going to ask our chief medical officer Dr. Zaks to take
that one.

DR. ZAKS: Thank you, Dr. Miller. Not as far
as we know. So let me make a few comments here. The
particles -- traces are gone by 48 hours, just to be
clear. They hang around for just a few hours. The
components of those particles, as far as we know, are
non-immunogenic in the sense that, as I described to
you, you’ve got the PEG with a lipid. Most of us are
walking around with antibodies against PEG, but they’re
not really meaningful in the sense of preventing
further utility of drugs.

And in fact, lipid nanoparticles, both by us
and other companies, are being used for routine
administration of other drugs and other experimental
medicine so far without any evidence of that kind of reactogenicity. So I don’t think we have any basis to expect that, neither based on our totality of preclinical data from our experience nor based on the history with these kinds of LNP medicines used in other applications. And those applications are even using much, much larger amounts and quantities, so in short, I don’t believe that’s the case.

DR. CHATTERJEE: Thank you.

DR. MONTO: And finally, Dr. Kim.

DR. KIM: So this is a question for Dr. Miller. I’d like to ask how you, Moderna, came about selecting 100 micrograms as the vaccine dose for phase 3. In your briefing material for phase 1, you outlined your considerations for comparing 100 micrograms to 25 and 250 micrograms, and in Study 201 you concluded that the data support of a two-dose schedule of either 50 micrograms or 100 micrograms for rapid induction of functional antibodies against SARS-CoV-2 and then selected the 100 microgram dose for phase 3.
What other considerations did you weigh in selecting 100 microgram over 50 microgram? And I ask this question because reports of any local reaction to the 100 microgram vaccine were around 70 to 80 percent in phase 3 and wonder what the safety profile might have looked like otherwise.

DR. MILLER: Yes. Thanks for that question, and I would like to emphasis that at the time the phase 1 study was ongoing. And when we had to select the dose to be able to start phase 3, the 50-microgram data were not yet available in the phase 1 study. Nonetheless, I mean, it’s hard to look backward and say what you would have done, but I’m not sure we would have taken a different decision. At the moment, we’re quite comfortable with the consistence and high efficacy that we’ve observed. But at that point in time, all we knew was that we were in the midst of the pandemic and we wanted to be sure that if we were going to undertake this large-scale safety and efficacy trial and we were going to expose people to a novel vaccine
that we had the best possible chance of demonstrating efficacy.

Another important point, as the 50-microgram data became available later and particularly in the subjects over 71 years of age, there was an indication that the 100-microgram dose was more immunogenic. And so knowing that the older age group is a group that is at significant risk for severe complications of COVID-19, that was another reason really to choose the dose.

And then the final reason is duration of efficacy is going to be important as we hopefully ultimately exit this pandemic, and we believe that the highest possible antibodies might lead to the longest possible duration of protection.

So for all of those reasons, the 100-microgram dose was selected. Nonetheless, again, recognizing that we are in a pandemic and now that we have data from the phase 2 available in 50 microgram doses, that’s why we put such emphasis on that correlative protection work we’re doing in the phase 3 study to see
if there may be possibilities for immuno-bridging based on that correlate in the future.

**DR. MONTO:** Thank you and thank you to Moderna and FDA for your presentations. Now, we’re going to be moving on to the item for Committee discussion without a vote, and is it possible to put up the questions? I’ll read them off while I’ve got them in front of me.

In considering Moderna’s plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in -- and let’s do this one at a time -- ongoing clinical trials -- so it’s ongoing clinical trials -- with the Moderna COVID-19 vaccine. And then we’ll talk afterwards about additional studies. So this is the ongoing studies. Let’s see. Dr. Gans?

**DR. GANS:** Thank you for this. So ongoing critical data, we still have multiple time points at which the Moderna is going to be collecting blood, and I think it’s a really missed opportunity, particularly
if they are actually collaborating with the NIH who have quite sophisticated ability to look at T-cell immunity, which we know is very important to maintain our humoral immunity and will be very, very important. So there’s two elements to this moving forward which I think are very critical: A, to get them any time points at which you’re collecting other blood samples -- so it was mentioned six months and further -- but specifically when there’s breakthrough. It’s going to be very important to be able to do the parallel T-cell studies to our B cells because if the B cells aren’t present, it’s going to be very important to understand what T-cell immunity was there that could be potentially boosted. So in both of those scenarios, that’s critical data in which to move forward and be able to understand this better.

The other critical piece of ongoing information that I think is going to be very important is to look at this idea of whether people who are vaccinated can continue to be spreaders of the disease.
And so looking in household contacts to see if there’s any disease in those individuals who are not prioritized to receive vaccine is going to be very important, so following those forward. And then lastly, doing the viral studies that are needed to be done within the vaccinated population, so continue to do those surveillance of the PCRS for RNA.

But it will be really important not only to look for the positive trends but the negative trends so we can understand that this is viable virus. So outside of the populations that they’ve already talked about in terms of ongoing, these are the critical things that I think are important. Thank you.

DR. MONTO: Thank you. Dr. Rubin?

DR. RUBIN: Thank you. I echo what Dr. Gans said and a couple more things. Antibody studies and T cell studies so we can look at correlates of immunity because that will be very, very helpful in the further development of the vaccine and for following waning immunity. So I think that those immunologic studies
continue to be important. And of course, monitoring asymptomatic infection, as Dr. Gans said, is critical, and, as has already been brought up -- and it sounds like it’s already a plan -- looking at escape mutants for loss of neutralization by the antibody or loss of T cell reactivity.

I do want to go back, though, to Dr. Goodman’s talk because that is all part of this. And the current -- it seems to me, at least, that the trial should have been designed as a blinded crossover study from the start. And my guess is that it’s relatively impractical at this point to do it, disappointingly, because it’s so late in the game, but I would encourage FDA -- I know it’s not quite a level playing field. But as new sponsors come in, I would encourage FDA to really consider that going forward. For now, I think they’re going to stuck with an open label study of the kind that Dr. Baden outlined. I’ll stop there.

DR. MONTO: Thank you for bringing us back to the nub of the question. Dr. Wharton?
DR. WHARTON: So I am particularly interested in continued safety follow up as well as follow up on the duration of protection. I think those are really critical factors that need to be taken into account as the study continues.

DR. MONTO: Any suggestions?

DR. WHARTON: Well, there will be opportunities to learn more based on other studies being done, but in terms of the ongoing clinical trials, it’s just important that the safety follow up be continued and that there be attention to the duration protection question.

DR. MONTO: Okay. Dr. Neaton?

DR. NEATON: Okay. Yeah. Thank you. So I want to go back to the presentation that Dr. Goodman gave this morning and also Dr. Baden. And I guess it’s all in reference to -- speaking to one factor, and that’s the durability of this vaccine. So it seems no matter whether you’re going to do a blinded crossover, as was suggested by Dr. Goodman, or you’re going to do
an open label kind of approach that Dr. Baden thought
was appropriate given the situation -- and practically,
that’s what could be done right now -- there’s an
opportunity to at least do immediate versus deferred
kind of vaccination of the vaccine subgroups which were
identified as at different risk, so the healthcare
workers, the high-risk older people.

And so I would take advantage of that because
right now there’s only 17 percent of the participants
that have 90 days of follow up, and I think additional
follow up -- which I guess is accruing right now
another couple of weeks -- I think we need more follow
up with this vaccine versus placebo to understand more
the kind of durability of protection. That’s what I
would suggest doing.

**DR. MONTO:** Thank you. Dr. Schooley?

**DR. SCHOOLEY:** Thanks very much, Dr. Monto. I
also want to emphasize that I think this planned
crossover study is a great opportunity to get some of
the data about durability of immunity in a very
structured way, and I’d encourage these sponsors to consider carefully constructed cohorts representative of the populations that are of most interest, ranging from age to gender, ethnicity and so forth, that would let us look at decay of both humoral and cellular immunity. The crossover would be a chance to reset the clock and get cellular immunity from the outset and to incorporate mathematical models to look at decay kinetics based on the induced immunity in individual people and decay across different groups based on their demographics and hypotheses about immunogenicity in different patient populations -- and to correlate that with viral shedding that is in break through cases, not just dichotomous data but quantitative data to get a good idea -- a better idea about durability of immunity and to start thinking about how this might play into studies later about when to boost and when to revaccinate because we know about the durability of coronavirus immunity in general. And there’s no reason for this virus to be any different.
DR. MONTO: Dr. Chatterjee?

DR. CHATTERJEE: Yes, thank you, Dr. Monto.

With regard to the ongoing clinical trials, my understanding is that there are pediatric trials ongoing, so this is not in reference to the trials that we were discussing today but certainly would encourage those trials to continue and for us to be brought those data. As far as pregnant women, my understanding, again, is that according to the criteria for inclusion, efforts were made to not include women of childbearing potential, but I think it’s critical given the workforce and the role that those women have in our workforce and the high risk that they incur caring for patients with COVID that the studies be also conducted in that population.

DR. MONTO: Dr. Sawyer?

DR. SAWYER: Thank you. I think in the ongoing trials we have an opportunity to learn more about asymptomatic infection in that a significant percentage of the study participants are healthcare
workers, and many healthcare systems are starting now to do routine testing of all healthcare workers. In my system, it’s every week. And I would encourage the sponsor to try to collect that data and make some comparisons between vaccine and placebo group.

**DR. MONTO:** Dr. Pergam?

**DR. PERGAM:** Thanks, Arnold. So I think two things that make sense to me is when they’re -- and I really hope that if there is this crossover design that they continue to do additional viral testing within those individuals because that’s a critical piece to know about potential transmission in that sub-cohort and particularly to look at viral load. I know that’s sort of a -- it sometimes can be a difficult process with nasal samples. But when we’re thinking about transmissibility and the levels of virus that are there, that might be one of the potential advantages of the vaccine.

I’m also curious within this study if Moderna could speak to us about some point about how many of
the 25 percent that are in the study that are healthcare workers have already opted out because they know they might be eligible to get the Pfizer vaccine. That would be an interesting piece of data. It might be too early to know that. That would be an interesting piece of data for us to know sort of what expectations might look like for other groups who may be deciding to go and get the actual available vaccine.

**DR. MONTO:** What I’m hearing from our members is two streams of discussion: additional studies that can be done whatever the specific design, unblinding with open label crossover design, and additional studies that might be done. I’m not sure how to bring the two together. What I think we might want to do in our discussions is to focus on what happens with the issue that I think is troubling to some of us, and that is the inevitable loss of the placebo group which occurs whatever you do, whether it’s unblinding and open label or a crossover design without unblinding.

Can we focus on that with some of our
questions? Then, we’ll get back to some of the additional immunologic shedding, viral shedding. This is a very difficult thing for us to do in a virtual setting. If we were around the table talking to each other, we could address these issues much more efficiently. But let’s try to talk about the placebo group first. And Dr. Gans, are you going to be talking about the placebo group?

DR. GANS: Yes. Thank you. I did want to just raise an important component that I think may the twist hasn’t quite been raised yet. We’re all concerned about losing that placebo group and really the integrity of the data moving forward, but I think we do realize that that is something that is going to be offered to individuals who got the placebo. So the only way that I see that we can really hold on to the integrity and continue learning something is to continue the blinding of the study.

So it doesn’t impact -- everyone gets what they want. It doesn’t impact the participants.
They’re all going to be vaccinated, and within six weeks everyone will actually know that they’ve fully been vaccinated. We need two doses, and we know that that’s what you need to be sufficiently immune -- you know, for this to be efficacious.

So everyone gets what they want. You can use the vaccine that actually now is coming to expiration, but you do it in a blinded manner. And in that way, you uphold the integrity and the ability to really look forward. It’s going to change everyone’s behavior otherwise, and that will actually impact the results.

So that is what I would plead to Moderna and to say that it seems that everyone gets actually what they want at that point. Thank you.

DR. MONTO: Thank you, Dr. Gans. Mr. Toubman?

MR. TOUBMAN: Can you hear me?

DR. MONTO: We can, yes.

MR. TOUBMAN: I’m thinking in a broader view of this that the study was funded in part by the taxpayers through Operation Warp Speed, and therefore
the government does have some ability to impose some
rules. And it seems to me there’s an assumption that
they’re just going to -- Moderna’s going to do what
it’s going to do, and it’s going to unblind the entire
placebo group. And it doesn’t have to be that way. We
haven’t been asked to vote on it, but we could vote on
it as well. But we could say that we don’t think it’s
acceptable for the Moderna plan to go forward if it’s
granted EUA.

And as just an example, it could be either you
do exactly what Pfizer is doing, and Pfizer ignored the
advice from Dr. Goodman, basically, last time -- do the
blinded crossover. So they’re not doing that.
Instead, they just unblinded the -- offered unblinding
to all the healthcare workers, and the other 80 percent
stay in the placebo. That’s one option.

Another option would be the blinded crossover.
But if we aren’t very clear that we think strongly that
that’s what should happen, one or both of those -- or
one or the other, then what’s going to happen is that
Modernā’s just going to do what it’s going to do, as happened with Pfizer. So I would strongly urge that we discuss the possibility of having a vote or directing what we think -- we’re only advisory. I totally understand that.

But if the Committee felt strongly that this is the way it should be handled in the existing study because of the worry about losing placebo folks, I think that would have significant impact with FDA, and FDA -- federal government dollars here -- could say these are the conditions upon the EUA being granted is we want the study to be maintained in a certain way.

**DR. MONTO:** You’ve raised some specific questions. I would urge the members to try to address some of these questions so we get a sense of the Committee. Dr. Meissner?

**DR. MEISSNER:** Mr. Toubman, I think that’s a very reasonable suggestion. Take a vote. Maybe give some support to Moderna. I would also like to go back to the point that Dr. Melinda Wharton raised and the
importance of having a blinded cohort in this study because eventually this will go for a BLA. And it will then be added to the vaccine injury compensation table, and it’s going to be so difficult to add this to the table without some evidence of well-established adverse reactions if they occur. And without a blinded trial, it’s going to be -- or a blinded group, it’s going to be very difficult to answer that question.

So what I would like to do is to ask Moderna if they have a sense of how soon they might submit a BLA to the FDA. Because once that happens, it’ll be the end of any randomized trial. And how quickly might the FDA turn around a BLA that they receive from either of these two companies?

DR. MONTO: Thank you, Dr. Meissner. You’ve raised some points that we may need some guidance from FDA and perhaps from Moderna as well. Dr. Gruber?

DR. GRUBER: Hi. Can you hear me? I’m sorry.

DR. MONTO: We can.

DR. GRUBER: Good. I just wanted to make a
comment regarding Dr. Toubman’s suggestion to turn this discussion point into a voting question. I believe -- I mean, we had discussed that -- if we should do this, but we decided because of the complexity of the situation -- and as you said, we have not only one. We have the two companies -- to not turn this into a vote at this time. We didn’t really ask this discussion point to be a voting question a week ago.

But I think what we would like to hear from the Committee -- and I have heard some Committee members here opining very clearly that some said we support the open label design or crossover that Moderna is suggesting. And others are pleading with really entertaining a blinded crossover. So if we hear the Committee members to speak out on these very specific issues, what they would suggest and what they think should be done, then I think we have reasonable guidance on the Committee on how to proceed in our discussions with the respective companies over the next couple of weeks.
In terms of BLA, biologics license application, and how fast we could move to that and what data we need, I mean, we all realize that the placebo-controlled blinded follow up is the gold standard of every clinical study that is conducted. At the same time, we do realize that it may at a certain point not be longer feasible. I think we would be, you know, working with the companies over the next couple of months to see what data do we need to support license application and what can be done.

And it is not only our -- and then I’ll stop. It’s not only the clinical data. It’s also the manufacturing information, the facilities information that will be very critical here and will be a deciding factor as to when we would be able to move to accepting the biologics license application. Over.

**DR. MONTO:** Thank you, Dr. Gruber. And I would urge the Committee members in their comments that are coming up when I recognize them to speak to some of these points. We’re trying to get a sense of the
Committee without a vote about some of these issues: unblinding, blinded crossover, or continuing whatever we can with a blinded placebo-controlled design. Dr. Fuller?

DR. FULLER: Thank you, Dr. Monto. So yes, that’s exactly what I wanted to comment on. It is a research (inaudible) when you want to get the best data you can, you must have the controls there. But in this case, these are people who may decide that they don’t want to stay in the study because it is such a severe issue. And so even if we kept the study as a blinded study and they’re not there, then we wouldn’t have the data that we want.

So I think Moderna has done a great job of designing their study so far. And if that’s what they recommend and because we want the people who are in the study to remain available and acceptable to get whatever data we can, I would probably go with the unblinding to keep them in the study to get what we can. And then the second point I want to make is --
DR. MONTO: And so when would you unblind?

Dr. Fuller, when would you unblind, before or after they become eligible based on the priorities?

DR. FULLER: I think I would unblind when the study has gotten from them what they need in terms of the timing. So if I were in the study and they told me “You are eligible in three weeks, but if you stay in, in five weeks or six weeks we will be able to get this much information. And we can make sure that you get this vaccine” -- so I guess it’s communication to me. And then, very quickly I do want to re-emphasis -- this was said earlier -- the important of having pregnant and lactating women studies here because that’s a huge piece of our population. So however we do it to make sure those people are kept in. Thank you.

DR. MONTO: Dr. Kurilla?

DR. KURILLA: Thank you. Gee. My -- oh, there we go. It’s actually working now.

DR. MONTO: It is.

DR. KURILLA: Yes. In terms of what we can
get out of the ongoing studies, I think we need to take
transmission off the table. That needs to be a
separate study. The two issues, I think, that we can
derive information about are the potential of
asymptomatic infections because if we actually are
inducing sterilizing immunity, that’s good. But if all
we’re doing is converting mild infection to
asymptomatic, that’s good, but it’s not as good because
there may be still ongoing transmission.

But the other more important thing to me is
duration. That’s the one issue that I’m most concerned
about with very, very limited data. The blinded
crossover would allow us to continue to collect
duration data, which I think is very important. But
it’s not going to permit asymptomatic infection data to
be accumulated, so we would lose that. And so I would
-- if there’s going to be a, quote, pseudo-unblinding,
the blinded crossover, I think, would be the way to go.

DR. MONTO: Thank you. Next is Dr. Moore.

DR. MOORE: There’s one question I have -- or
it’s not a question. It’s a comment, and I don’t really have an answer for it. But with two large vaccine trials that are now currently blinded and they’re ongoing, the vaccines are shortly going to be released publicly in some way, or at least Pfizer has been released. That suggests that there’s going to be some people that are blinded in, for example, the Moderna study who are in the study because they’re personally, tremendously afraid of getting COVID. And they may move over to get vaccinated. And if they’ve already been vaccinated, then we have a risk of over-vaccination and also adverse events occurring that we don’t recognize are actually due to the fact that people are not being vaccinated according to the protocols that we have. I don’t have an answer -- I don’t have an answer to whether it’s better to unblind or blind to address that question.

But the other point is, is that I do disagree with Dr. Kurilla. I do think that transmission is perhaps the most central thing that we need to address
as of right now in this epidemic and to try and get our
best handle on that probably is not the nasal or the
nucleocapsid antibody but rather direct detection of
nucleic acid. So that’s one reason why I’m pushing for
repeated NP swabs.

More importantly than that, perhaps, is, even
if we don’t have an answer as to whether these vaccines
do limit transmission, is that I would hope that both
Moderna and Pfizer would work with public health
officials to try and establish (audio skip) with their
well-defined cohorts. For example, are there protocols
for (inaudible) vaccination that we could use that will
work or have the best chance of working? Because
ultimately we anticipate that by next summer we will
have a low rate of transmission, and then we will be
putting out fires. And we need to know how to put out
those fires with these vaccines if they do interrupt
transmission.

DR. MONTO: Okay. Dr. --

DR. KURILLA: Arnold, can I just respond real
quickly to Patrick’s comment? I didn’t mean --

DR. MONTO: Okay. Very quick.

DR. KURILLA: -- that transmission isn’t important. I simply meant that I don’t think you can get it out of this trial design.

DR. MONTO: I understand. Having done a lot of observational studies on transmission, I tend to agree with you. It’s a very difficult thing to study unless you’re studying that -- that subject. Dr. Cohn?

DR. COHN: I just wanted to add to Dr. Fuller and other’s comments that I agree that Moderna’s plan sounds reasonable, especially given the logistical challenges that a study sponsor would potentially face in terms of when a particular individual in the study becomes eligible. I think given the variability that will happen at the state and local level in those criteria it would be hard for them to implement that across the board. And I also believe that given the large number of observational studies that are being implemented in combination with multiple different
groups that some of these questions, while it’s not
perfect to -- while a clinical trial blinded would be
ideal, I think that if you can look at some of these
questions from a multitude of other observational
studies, we will be able to understand -- we’ll be able
to answer some of these questions through a similar
degree of confidence.

DR. MONTO: Dr. Offit.

DR. OFFIT: Right. Just to get to Dr. Kurilla’s point, there is an ongoing trial that is
being planned for early next year on college campuses
where people will be vaccinated or not. And then those
that are vaccinated will be followed to see to what
extent they’re contagious by doing extensive contact
tracing, which is really the best way to do it, as Dr.
Monto alluded to, and then look at these sort of -- you
know, the nasopharyngeal secretions to see if you can
eventually have a biomarker for what that
contagiousness is. But that is being planned and
apparently is being funded, so good news.
DR. MONTO: Dr. Moore. Again, let’s try to get a sense of the Committee about the unblinding/crossover issues.

DR. MOORE: I didn’t hang up my -- I didn’t have a question. Sorry.


DR. PERGAM: Yeah. So I think I really like Dr. Cohn’s comment. I definitely like the idea of continuing the blinding portion in the crossover design because of the advantages it gives you in terms of following placebo individuals, but I think the realistic piece of this and the challenges that will entail for the differential groups in terms of when they will get access to vaccine will make this really difficult to do. And I worry in terms of different states and their approaches to this that that will be difficult.

So I’m sort of -- I was leaning towards the side of we would be doing blinded because that would
provide some real advantages. But I think in some ways
the realistic aspect of this really makes this -- going
to be difficult, so it may be impossible to approach
that side. So I think in an ideal world I think we
would like to keep a blinded -- the blinded portion of
the crossover design, but I think the reality of what’s
happening may make that two difficult to do.

DR. MONTO: Thank you. Dr. McInnes.

DR. McINNES: Thank you. I’m in favor of the
blinded crossover approach. I think it’s powerful, and
I think we may have a little bit more time than we
actually think. I could imagine it’s an area where you
could articulate the priorities, and it could be even
on a state level. I don’t think there’s going to be
this much vaccine floating around for a few weeks. So
even though people may want to walk and get in the
queue to get an EUA, I’m just not sure what the supply
is going to look like. And you may have a little bit
more time than we think.

So I think in principle I like the blinded
crossover. I think it’s powerful, maybe the best we can get in terms of being able to continue to assess safety. I think the crossover could be tailored to a particular geographic area. I’m not saying it’s easy to do, but I would entertain it.

And my third point is we’ve been talking about pregnancy registries, and I just want to iterate that what I think we’re talking about is pregnancy exposure. We’re not actually proposing a pregnancy registry but for exposure of FDA regulated products. So those are my three points. Thank you.

**DR. MONTO:** Thank you. Dr. Toubman [sic] has a suggestion for us.

**MR. TOUBMAN:** Thank you. Right. So I do have a suggestion for framework of discussing this, but I think we addressed the ethical issue. There’s really no ethical issue with not -- with having to unblind these folks. They don’t have to be.

So the issue is really, I think, boiling down to what’s practical, what’s workable. And I guess when
people say it’s not feasible to maintain those who are
not in priority groups in the blinded study, you’re
saying that what Pfizer’s doing is completely
impractical because that’s what they’re doing. What
they’ve told all their folks, at least in my state -- I
assume it’s the same letter everybody got -- is that
“The vaccine transition option is a voluntary process.
It offers all participants 16 and older in the placebo
group an option to transition to the vaccine group.
Interested participants can transition at two time
points. To determine the order in which participants
can begin the vaccine transition option, Pfizer and
BioNTech are following the guidance of the U.S. Center
for Disease Control Advisory Committee for Immunization
Practices, ACIP, which has prioritized healthcare
workers for direct patient contact.”

Now, there’s also commentary that we got. You
know, there’s 148 of current trial participants who
specifically recommend -- they’re fine with saying
that, as a vaccine developer achieves EUA, it should be
permitted and, indeed, encouraged to unblind members of
the placebo arm who would naturally qualify for
vaccination under their state vaccine distribution
plan. Dr. Cohn pointed out there’s variance, and I
understand that. But all we need is a few more weeks.
If we just can get a few more weeks of data by
maintaining placebo control for those who are not in
the priority groups -- and that will be in this case
for Moderna 25 percent will go out as healthcare
workers -- then we gain a lot. So it is feasible, or
if you’re saying it’s infeasible, you’re saying that
what Pfizer’s doing is not feasible.

And I think a last point here -- and Dr.
Goodman explained this -- there’s a real reason to have
uniformity here between the different sponsors. And
since Pfizer’s doing this, there’s no reason -- there’s
no ethical problem with having Moderna follow the exact
same practice -- protocol. So my suggestion would be
that we recommend that Moderna do what Pfizer’s doing
because it is feasible for a period of time, just a few
weeks, which would be really helpful. And then the secondary thing would be support for the blinded crossover.

DR. MONTO: Okay. I’ve been asked by Committee members if we are going to have a vote on this. My sense, Marion, from what you’ve told us is that you would rather we did not and just give you the sense of the Committee. Am I correct?

DR. GRUBER: Yeah. You’re correct, and I really thank the Committee for being very clear here over the last couple of minutes to really speak out on their preference. It is complicated, and I was trying to sort of keep a tally a little bit here on what I was hearing.

DR. MONTO: So was I and having great difficulty because there were nuances.

DR. GRUBER: That’s right. You know, I -- again, I feel that -- I’m speaking here for the Office of Vaccines, but at the same time, I have not had a chance to confirm it with my colleagues. So if you
could give -- if you could continue the discussion for a bit longer because I don’t think that all the Committee members really opined here, and I would like to take a minute to get some responses because I asked the question of my Committee members -- of my people here to weigh in with their opinions on this as well. So if you could spend maybe a couple of more minutes discussing this very important question.

DR. MONTO: Right, Marion. We’ll talk among ourselves about this, but I just want you to think about, if we do have a voting question, what that would be because I’m not clear. This is not a black and white issue.

DR. GRUBER: Yeah. I know. I know.

DR. MONTO: And I’m not clear what the vote would be about, so please, if this is going to be a voting question, let’s have a clear question because I’m not sure -- we don’t want a lot of abstentions and things like that. We’d defeat the purpose.

DR. GRUBER: This is why we tried to --
DR. MONTO: Right. I understand. That’s why you didn’t want to vote in the first place.

DR. GRUBER: Yes.

DR. MONTO: Because it’s so difficult. Could I ask all the hands to be lowered, and those people who have not spoken on this question -- because that’s what we’re hearing -- please try to tell us what they would think about it? I see Dr. Hildreth.

DR. HILDRETH: Dr. Monto, are you inviting me to comment?

DR. MONTO: Yes, please, Dr. Hildreth. If you’ve got a comment and an opinion, we’re looking for opinions. Opinions are usually pretty cheap, so let’s get them from everybody.

DR. HILDRETH: Sure. I want to express my strong support for the plan that was outlined by Dr. Baden to have an open label crossover. We can still get a lot of information about safety. As a matter of fact, I totally agree with him that the participants who got the placebo should not be disadvantaged
because, after all, we are still under a national health crisis. And the whole point of this was to get a vaccine that could be used to slow down COVID-19. So I have strong opinion that it might even be unethical for us not to offer the vaccine to the placebo recipients, and I agree with him that if we would do that --

DR. MONTO: This would be -- right. This would be right now or when their priority group comes up if that’s feasible?

DR. HILDRETH: For me, it would be okay either way. When their group comes up, they should be given the opportunity to get the vaccine. I just really feel strongly if we don’t do that we’re going to lose the placebo participants and maybe do harm for future recruitment of vaccine trials. So I just think that I agree with his plan for an open label crossover, and that’s what I would recommend to the FDA. Thank you.

DR. MONTO: Dr. Sawyer?

DR. SAWYER: So the point was brought up...
earlier that people -- the blind is already going to be severely eroded by the local and systemic side effects of the vaccine. And I think now that that information is being widely publicized in the media people are really going to figure out whether they got vaccine or placebo. If you got two injections and each time your arm hurt and you got malaise the next day, you’re going to figure out that you got the vaccine. So I think behaviors are going to be modified based on that, and so I’m -- my opinion is the blind is already eroded to the point where it probably won’t matter. So I’m going to support the crossover approach, and I prefer the crossover approach to allow people to be vaccinated when their tier comes --

DR. MONTO: That’s blinded. The crossover is blinded.

DR. SAWYER: No, I’m supporting nonblinded crossover.

DR. MONTO: You’re supporting an open label, then.
DR. SAWYER: Open label crossover but when the people come up in their tier.

DR. MONTO: Okay. Dr. Wharton?

DR. WHARTON: So since I didn’t really specifically address this point when I spoke earlier, I wanted to say that although the blinded crossover seems really powerful and has a lot of -- and seems very valuable, right now healthcare workers being vaccinated in many different parts of the country, and to ask the 24 percent of healthcare workers in the placebo group to go unvaccinated while a blinded crossover change in the protocol was implemented really doesn’t seem feasible to me. And it is preferable that people be kept in this study, and that can best be done by offering vaccination in the appropriate tiers as they come up. And additional data can be collected on those vaccinated persons as the study continues. So that would be my suggestion.

DR. MONTO: Thank you. Dr. Rubin?

DR. RUBIN: I’m going to echo Dr. Wharton, but
I wanted to go a little bit farther saying that the open label study is -- seems like the only choice. But it’s not a terribly good choice, so I think we should -- it’s better to keep them in a study. But for future sponsors and for future trials, you can derive a lot more information out of the crossover design particularly around AEs. That’s what I think we’d learn a lot more about, so I would favor that in the future. But I’m supportive of an open label trial now.

DR. MONTO: I agree. And the problem is we’re dealing with an unprecedented situation, and there are a few things that people didn’t think about going in. Dr. Sylvester?

DR. SYLVESTER: Yes, thank you, Dr. Monto. I agree with what Dr. Rubin just said. I think that it’s not a perfect world. The open label makes sense at this point and time, and maybe in the future we ought to be thinking about the crossover that’s blinded. I’m worried also that with a greater than 90 percent vaccine efficacy will people enroll in future vaccine...
trials knowing that they’re not going to be able to get it? So I think the inevitability towards the crossover makes sense, and let’s work on this one at this point. So I’m in favor of open.

DR. MONTO: Dr. Meissner?

DR. MEISSNER: Thank you.

DR. MONTO: Any further comments? I know what you said before.

DR. MEISSNER: Yeah. And after listening to this fascinating discussion, it’s very hard to reach a conclusion. I will just say that this will be -- if we don’t do the blinded crossover, this will be the last opportunity because once a vaccine is licensed, no more placebo-controlled trials. So we will be throwing out that opportunity. Now --

DR. MONTO: If I could interrupt, I think that’s one of the reasons we have question or discussion item number 2. What in the world do we do to collect in the future placebo-controlled data?

DR. MEISSNER: Yes. At least in the United
States, that will be very --

DR. MONTO: Well, that brings up another question.

DR. MEISSNER: Yes. And also, it’s going to - -
what is this going to mean for the other vaccines when they start their -- or are already in their phase 3 trials? Will they follow the same regimen that Moderna and Pfizer follow and there won’t be the option of a blinded crossover because why would a subject participate in that trial if she or he could get an authorized vaccine? And I think that what Dr. Sawyer said is also true. And remember, anyone who wants can go out and get an antibody test and find out whether they got the vaccine or the placebo, so it’s not --

DR. MONTO: That too.

DR. MEISSNER: It’s not that secret. And I think Dr. Cohn’s comment about practicality is very important. So I would still prefer a blinded randomized crossover, but it’s also going to be very, very hard to do that. Over.
DR. MONTO: Thank you. Dr. Perlman?

DR. PERLMAN: Yeah. So the only thing I would -- I would agree with all the panel’s discussion. I just wanted to give my opinion. I like the blinded crossover, but it sounds like it’s not going to be feasible because of this ability for people to just walk into the vaccine limb, particularly people who are in healthcare settings now. So if it could be instituted immediately, that would be one thing, but it doesn’t sound like that’s really going to happen.

That’s, I think, what Dr. Baden was saying this morning -- that it was logistically going to be very difficult to do that. So that’s why the Moderna approach may be the best.

DR. MONTO: Dr. Kim?

DR. KIM: I don’t have any specific reason to add to all the discussion that’s taken place already, but I just want to go on record in saying that I would support the open label.

DR. MONTO: When? Right away after the EUA
or after the individual’s priority group comes up?

That’s what Pfizer is doing. Okay. Let’s move on to
Jim Neaton. Dr. Neaton?

DR. NEATON: Yeah. I prefer the priority
based unblinding. I mean, this morning it was pointed
out that there’s nothing in the consent about -- that
you get the vaccine, once the study’s over with, if
you’re in the placebo group and it’s effective. But I
think all consents have a requirement to explain the
data to the people, from the trial that you’re in, and
its implications for them. That and the press that
this trial, and the Pfizer trial, and the AstraZeneca
trial have already received I think makes it very
difficult, plus the local circumstances of healthcare
workers being vaccinated.

So I think try to maintain the blind between
the vaccine and placebo as long as possible. Try to
keep the people in the cohort because you want to
follow everybody for another two years. But in order
to do that, the practicalities, I think, are such to do
it in some type of a stage by priority kind of setting
if people can structure it that way.

DR. MONTO: Dr. Schooley?

DR. SCHOOLEY: You know, as much as we’d like
-- as I’d like to see things remain blinded as a
scientist, I think from the factual perspective and
from the perspective of the realities of vaccine
availability and logistics, we need to realize that the
trial participants are going to want to know what they
were in. They’re going to walk if they don’t know, and
I think it’s really important to keep them in the
trial. So I would support an unblinded crossover.

I think we have to also -- I think it’s going
to be complicated trying to understand when the vaccine
is really going to be available in each location with
the way our country works, and it will take some time
to get the logistics of even the unblinded crossover
set up in a synchronous way starting today. So I would
favor going ahead and beginning to make those changes
in the bureaucracy and then being ready to do it when
it’s in place in a synchronous way as best we can with
the bureaucracy we have to deal with.

**DR. MONTO:** Dr. Cohn and then the final word
from Dr. Toubman [sic] before we look very briefly at
the second point.

**DR. COHN:** Just to clarify what I said
earlier, I think you can very easily separate out the
healthcare workers from the other groups, but there’s
not going to be some sort of “This person is going to
be eligible now.” Health departments will be opening
up vaccination for different groups more organically,
so I think if you could vaccinate the healthcare
workers now, like Mr. Toubman said, and keep the blind
for a majority of participants for several more weeks -
- I think if a participant believes they’re in a group
that is now being recommended for vaccination, the
sponsor should not be policing that, similarly to how I
don’t think health departments will necessarily be
policing that. So that just clarifies my previous
comment.
DR. MONTO: Dr. Lee?

DR. LEE: So I would agree with the open label. Although normally I would suggest the prioritization, I would agree with Dr. Schooley that it’s such a hodgepodge here it’s impractical. And the other consideration I think we need to keep in mind in starting this as soon as possible is they do have this drug supply that apparently they have available that they could use for this purpose, which has something of an expiration date. But I favor the open label crossover. Thank you.

DR. MONTO: And quickly Dr. Chatterjee.

DR. CHATTERJEE: Yeah. My comment, Dr. Monto, was actually about the other studies. It’s not about this first --

DR. MONTO: Okay. Why don’t you wait for a minute while I recognize Dr. Toubman [sic], and you can kick off that discussion?

MR. TOUBMAN: Thank you, Dr. Monto. By the way, it’s not Dr. Toubman; it’s just mister.
DR. MONTO: It’s Mr. Toubman. I keep trying, but we do it by a knee jerk reaction.

MR. TOUBMAN: Thank you. I just wanted to see if I have this right from just listening to folks. It sounds like there’s some disagreement, but predominantly people are okay with open label. But I didn’t hear anybody objecting to the prioritization, meaning that, yes, you unblind, but you do it when their group comes up.

We just heard there is -- obviously, there’s some variance in states, and there’s going to be some problems with it. As Dr. Cohn pointed out, healthcare workers are a very clear group, and the other groups when we get to them are going to be not so clear. But Pfizer believes that that’s doable, so we can at least try it. They can try it, and to the extent it doesn’t work, it doesn’t work.

But in the meantime, since people aren’t going to be able to access vaccine now anyway for a period of time if they’re not healthcare workers or nursing home
residents, then we gain something by saying, yes, open
label but when their group comes up. And also, we
avoid any ethical issues by doing that.

DR. MONTO: Dr. Gruber, do you have some
comments?

DR. GRUBER: Yeah. I just wanted to make a
brief comment. I had the chance to confer with some of
my colleagues, and the consensus is, as I stated
before, that we will keep this question as a discussion
point. And it should not be voted on. Thank you.

DR. MONTO: Thank you. And Dr. Chatterjee,
you had a comment to start us off on what happens if we
don’t have a placebo group -- what other additional
studies can be done.

DR. CHATTERJEE: Yes, thank you, Dr. Monto.

DR. MONTO: And we don’t want any open
discussion of all the observational studies to learn
about how vaccines work but focus on this current issue
of the lack of a placebo group.

DR. CHATTERJEE: Okay. Well, what I was going
to talk about was actually additional studies such as co-administration of other vaccines.

DR. MONTO: Okay. That’s on the table. I didn’t want to get into studies of transmission and things of that sort. Okay. Please. Please go ahead.

DR. CHATTERJEE: I’m not sure if I should continue.

DR. MONTO: Yeah. Please go ahead. Yes, please.

DR. CHATTERJEE: Okay. Other populations that should be studied I thought should include older adults, those who are 75 and above, because the numbers of participants in that group I think are relatively quite small and then also residents of long-term care facilities. And I’m not sure that those folks were included in these trials.

DR. MONTO: Thank you. Very helpful. Dr. Hildreth.

DR. HILDRETH: I’m here. I was going to -- I agree with the previous comment that it would be nice
to do some studies in people living in assisted living facilities since that wasn’t specifically part of this. And that’s a crucial group that we need to have some data from. Thank you.

DR. MONTO: Dr. Pergam?

DR. PERGAM: Thanks. I have to say I completely agree with Dr. Chatterjee. One of my concerns was the small number of elderly patients in the 75 and older. That’s important. We need to expand on that. I also --

DR. MONTO: What were the -- let me just ask you. What would the design be because we can’t do a placebo-controlled design?

DR. PERGAM: Yeah. I think it’s --

DR. MONTO: How would you study that?

DR. PERGAM: Yeah. I would study it just as potentially immunogenicity alone. That might be sufficient. I mean, it’s probably -- we can’t do -- we can’t do a placebo-controlled design, but I think you at least have the data from the primary trial to see
what immunogenicity looks like between the two. And I think that’s probably going to be the best you could do.

I think that’s also true in the immunosuppressed population, which I think is a really -- I know they are working on these trials, but I think that’s going to be really important. There aren’t going to be the ability to do placebo-controlled trials in that sense, and I think you’d have to look at immunogenicity as well. So you’re looking at patients who necessarily can’t produce as robust an immune response and see how much less of a response you’d get in those groups. I think those are going to be really important studies for the larger population, particularly since immunosuppressed patients will make up 4 to 5 to even 6 percent of the entire U.S. population.

**DR. MONTO:** Thank you. Dr. Gans?

**DR. GANS:** Since we’re talking about other studies, a couple of points that haven’t been raised.
I’m trying not to repeat things, but I know that there’s a lot of overlap here. The other studies that we actually haven’t talked a lot about are really looking at other conditions. We talked about Bell’s palsy, but there’s other neurologic outcomes that I really think have to be high on the list. So we really need to consider, especially when we go down into the children studies -- so I want to urge those particular things to be looked at.

The other part of it is the cardiac findings. We think most of this -- likely from the SARS-CoV-2 receptors there may be specific to the virus, but we haven’t figured out if their immunologic or not. And we’re seeing a lot of different cardiac manifestations. So this needs to be studied not only just as potential outcomes of the disease versus the vaccine but also in people with cardiac disease, so I think that’s a really important piece to keep in the forefront as we’re moving forward and to think critically about.

In terms of some of the studies that need to
happen, again, we talked about some of the immunologic studies, but studies in children, I think, are going to be particularly important because we can extrapolate, particularly studies that we’ve done in children where the T and B cells do not follow the same pattern as each other and as an adult because they have different maturation of particularly the T cell responses. And therefore, it’s going to be really important as we understand this to really -- I want to just reiterate really doing those studies ongoing. Thank you.

DR. MONTO: Thank you. And next, Dr. Sawyer.

DR. SAWYER: One of the things we eventually need to learn is what happens if you get one dose of the Pfizer vaccine and then a second dose of the Moderna or vice versus. That mistake is going to happen a lot as we start to disseminate vaccine around the country. The interim guidance that’s been issued so far to immunization registries is to not give a third dose, in other words to assume that, even though you’re mixing products, that’s an adequate -- you’re
going to get an adequate immune response. So at some point, it would be nice to know if that’s really true.

DR. MONTO: Dr. Rubin.

DR. RUBIN: I know that we’re not supposed to propose other studies, but again correlates of protection are going to become extremely important in investigating a non-placebo --

DR. MONTO: That’s okay.

DR. RUBIN: Okay. Correlates of protection are going to be really important in interpreting these trials because of the lack of placebo. We’re going to have much more difficulty assessing safety, and there’s no easy way to do that when we have no placebo-control. But we can at least get at efficacy if we have some good idea of what protection looks like.

DR. MONTO: Dr. Lee?

DR. LEE: I think one of the interesting things we might want to consider that does not require placebo control is a non-inferiority trial of two doses versus one because I think you’re going to have a
certain subset that doesn’t get the second dose. And if you have reasonably good vaccine efficacy with one dose, then I think we really need to think about that. So just we would be looking at it pretty much at the incidence of COVID-19 in the two groups. But I think a non-inferiority one would be really one to think about. Thank you.

DR. MONTO: And how about different doses? We hear some questions raised about the dose that was suggested or the timing of vaccination.

DR. KURILLA: Especially for children, Arnold.

DR. MONTO: Especially for children. I’m trying to get a discussion going. It’s hard virtually. Dr. Kurilla, was that you?

DR. KURILLA: Thank you, Arnold. Yeah. Let me just echo Dr. Rubin’s point about the correlates of protection. I think this is probably one of the most critical features not just for this vaccine but for future vaccine trials. It will really make other vaccines realistically approachable in terms of their
clinical trials going forward. If we could move
towards some sort of accelerate approval, the
immunogenicity I think would be a very good endpoint in
that work.

The other thing in regards to the one versus
two doses, I think that’s an important trial, but I
would also like to emphasis that in the follow ups that
what’s being done, this sort of surveillance for under
the EUA, I think there needs to be some aggregated date
to look at who only got one dose because there are
going to be people who are not going to come back for
that second dose and to see whether there are any clues
that may be quite informative without having to go
through a formal trial to sort of get an assessment as
to whether that’s a feasible approach.

DR. MONTO: Dr. Schooley.

DR. SCHOOLEY: I just wanted to reemphasis the
immunocompromised patient population, not just because
we need the data but because they also are a place
where we can have a wider spray -- splay of immune
correlates to look at and might get some correlates of immunity data in a relatively short period of time if they are starting at a lower point in terms of their vaccine induced immunity.

**DR. MONTO:** All right. Immune correlates are a recurring theme, and it looks like we may be blessed with an immune correlate here with this vaccine, which we haven’t seen with other vaccines. And clearly that’s a message that immune correlates are paramount.

**DR. GANS:** Thank you. I just wanted to follow up on a thought. I kind of mentioned it in my last comment, and I think Dr. Offit had started out with this -- is as we’re investigating this disease further and we know that hopefully populations get immunized, one important component will be to look at the adverse events as they follow in natural disease versus the adverse events that follow vaccination because, as we all know, vaccination is highly protective, although often not 100 percent. But as long as they reduce the
actual events of the severe adverse events, then
actually that should be an issue of protection that is
studied ongoing, so for instance the Bell’s palsy and
other of the outcomes that we’ve seen. Thank you.

DR. MONTO: Dr. Sylvester?

DR. SYLVESTER: Yeah. Dr. Monto, you raised
an interesting question about the timing between the
doses. And I think that there’ve been some interesting
studies that we’ve seen in the vaccine world where the
longer you wait for your second dose the higher your
antibody levels may be. I think the practicality of
that in a pandemic may be difficult.

I think people are going to want to line up,
and Pfizer’s got a three-week window. And Moderna now
has a four-week window. I don’t think many people will
say “I’ll just wait eight weeks or 12 weeks before I
get my second dose.” So I like the question, and it’s
a great academic question. I’m not sure in a pandemic
it’s a practical one.

DR. MONTO: Dr. Gans, is that -- no. Dr.
Pergam.

**DR. PERGAM:** Thanks. You know, Arnold, the dose issue that you brought up is a really important one that I want to come back to because, again, thinking about populations that tend to have less response to -- or less side effects, it looked like the older population had less complications from the second dose of the vaccine, which might suggest they could tolerate a higher dose. And we’ve seen in other vaccines that higher doses are more beneficial for -- whether it’s zoster, whether it’s influenza, it could be beneficial. And so it could be a real value in targeting those populations with maybe a slight difference in immunity, either the immunocompromised population or the older population, as targets to do studies looking at higher dose. And I know Moderna had the -- I think the 250 was the highest dose. I think that’s right -- would be at least an option to try and see if there was better outcomes in immunity from the higher dose of the vaccine in those groups.
DR. MONTO: Thank you. Dr. Perlman and then finally Dr. Fuller before we go on to the voting question.

DR. PERLMAN: Yeah. So I just wanted to reinforce the idea of doing a pediatric trial and also pointing out the problems because children don’t get much -- don’t get particularly sick with this. So it’ll be very important to think about whether we’re going to measure serial serology, serial culturing. And for little children, this will be very hard, but I think this is really important because this may be the major group that’s unvaccinated in a short time.

DR. MONTO: Okay. And Dr. Fuller, final comment before we discuss the voting question.

DR. FULLER: Yes, thank you, Dr. Monto. So looking really far ahead, a couple questions which have to do with duration of protection. What will happen if this vaccine isn’t a lifelong vaccine, which we expect that it is not? So how will we know when somebody needs a boost, or how will we know if they’re protected
against new strains that may evolve from coronavirus?
And I know that’s not an easy study to design, but I
just want to put it out there because if we really want
to co-exist with this virus or variations thereof, we
need to be thinking about those sorts of things.

DR. MONTO: Thank you all for this very
vigorous discussion. I think we have given FDA a sense
of our wish that we could do a crossover blinded design
but the realization that that may be impossible. We
know what Pfizer has proposed, and FDA will be
negotiating with Moderna about the way they will
address this problem. So I think we’ve really had the
time, fortunately, to go over this in the kind of
detail that it really needs.

Now, we’re going to have a discussion of the
voting question. We will then have an electronic vote,
and then I will ask the Committee members who wish to
explain their vote -- don’t need it from everybody --
to explain their votes. So the question is, based on
the totality of scientific evidence -- it’s very
carefully phrased. Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older? So hands up for commenting as you wish on this question. Dr. Gans, you were the first.

**DR. GANS:** Thank you. Thank you for allowing us just to opine about this really important topic. I think that this is a really opportune time for us to move science forward, and I would say that the evidence that has been studied in great detail on this vaccine highly outweighs any of the issues that we’ve seen. And I think it really supports us being able to, with the pandemic in our background, really move forward and finally provide a safe and effective way to get to herd immunity. Again, understanding that this is for 18 years and older and that obviously we need to be able to provide this to all of our population to get there, but it’s a first step. Thank you.

**DR. MONTO:** Thank you. Dr. Kurilla?
DR. KURILLA: Thank you, Dr. Monto. Yeah. I have some serious reservations about this question because we’ve been discussing -- this whole meeting has been focused on the emergency use authorization for this vaccine, not for full approval under a BLA. And the question really doesn’t reflect that. It could easily be seen as full approval.

There’s quite a bit of confusion, I think, not only in the general public but many in the media reports of last week and this week talk about this panel approving the vaccine or recommending this vaccine for approval. And we even heard today during the open public hearing session several medical professionals who talked about approving. I think that the distinction between an EUA product, which is still an investigational product, and the full approval -- a product under full approval with a BLA is a distinction we need to maintain. And I think we’re losing that simply by looking at this as an age related -- anyone over the -- 18 years of age and older.
It doesn’t strike me as really addressing the emergency, which is severe and serious life threatening COVID disease in specific populations. So I have a lot of problems because this could be interpreted as us actually recommending full approval of the vaccine. And in the minds of the general public, that may happen and may preclude adequate -- not only adequate evaluation of this vaccine but other future and ongoing COVID vaccines in development.

DR. MONTO: Thank you. I appreciate your concern. I wonder if Dr. Gruber could address amending the (audio skip) because (audio skip) the emergency use authorization. But the question doesn’t really state that.

DR. GRUBER: So when we published the agenda for this VRBPAC Committee meeting, the topic is “The Committee will meet in open session to discuss emergency use authorization of the Moderna COVID-19 vaccine for the prevention of COVID-19 in individuals 18 years of age and older.” So that is the topic of
today’s VRBPAC discussion.

It is to discuss emergency use authorization.

That’s what the agenda says. We phrased this question the way we phrased it because, as was stated, a vaccine authorized under an EUA is a product that has not been approved. It’s a non-approved product. And under the EUA, in order for us to lend or issue an EUA, we have to make a determination that the benefits of the product outweigh its risks. Does that --

DR. MONTO: Marion, what if we just add the words “EUA -- under an EUA” to this voting question? Would that be possible?

DR. GRUBER: Based on the totality of scientific evidence available, do the benefits of the Moderna COVID outweigh its risk for use --

DR. MONTO: For use under an EUA in individuals --

DR. GRUBER: For use under an EUA in individuals 18 years of age and older? We can do that.

DR. MONTO: Do you have to take this to your
lawyers, or can you make a determination?

DR. GRUBER: We can do that. We can say, “For use under an EUA in individuals 18 years of age and older,” if the Committee needs that clarification. Then I think we can safely do so.

DR. HILDRETH: Dr. Monto, may I make a comment?

DR. MONTO: Yes. Yes, please, Dr. Hildreth.

DR. HILDRETH: The question is very clear. Do we think that this vaccine’s benefits outweigh the risks? And if we think that, then the FDA will make a decision as to whether or not to issue an EUA. That’s not what we’re voting on. We’re voting on whether the benefits of this vaccine outweigh the risks, and then it’s up to the FDA to make a decision as to whether or not they’re going to issue an EUA. So I think the question should be left exactly as it is.

DR. McINNIES: I completely support Dr. Hildreth.

UNIDENTIFIED MALE: Ditto.
DR. MEISSNER: Dr. Monto?

DR. MONTO: Okay. Yes, please.

DR. MEISSNER: Cody Meissner. Dr. Gruber, I have a little trouble with it the way it’s written also because it’s going to be very hard to study other vaccines -- experimental vaccines -- when a person looks at this sentence. And what I would suggest is that we write “through two months of follow up,” or put some qualification in there that defines the length of time that it’s been evaluated. Because this is a blanket statement that everybody over 18 years of age should get it.

DR. GRUBER: No, this is the question that is phrased the way it’s phrased because we want to know if under an EUA whether the vaccine -- the product is still considered a nonapproved product but needs to -- could be given during a public health emergency if the benefits of this product outweigh the risks. It does not imply that under an EUA, then, of course -- if we determine that the benefits outweigh the risk under the
authorization -- under an EUA authorization, it can be
given then to individuals 18 years of age and older.
But that does not equal that the product is approved.

    DR. MEISSNER: But a lot of people won’t
understand that thinking. Could you say at least “this
experimental vaccine?”

    DR. MONTO: No, no.

    DR. GRUBER: That too --

    DR. MONTO: No. I think once we start
qualifying in terms of the duration or anything like
that, it’s going to be so confusing because the
duration may get longer as we go forward.

    DR. MEISSNER: Arnold, let me offer an
alternative. Marion, instead of an age --

    DR. MONTO: Okay. Well, you offer an
alternative, and --

    DR. MEISSNER: -- what about “people at risk
for serious COVID disease”?

    DR. MONTO: No, no. And let me just say that
we have a question now. We are advisory to FDA. They
have put in a question that they feel comfortable with.
Am I correct, Marion? And that is what we are voting
on. If the vote is not in favor, then we can discuss
this further. Marion, how should we proceed?

**DR. GRUBER:** I would like to proceed with
keeping the voting question as currently phrased.

**DR. MONTO:** Okay. There it is.

**DR. FULLER:** Dr. Monto, may I ask a question
not about the phrasing?

**DR. MONTO:** Excuse me. Dr. Hildreth? Yes.

**DR. HILDRETH:** Are we going to go back and
retrospectively change the question we voted on for
Pfizer?

**DR. MONTO:** Well, that’s another issue I was
thinking of.

**DR. HILDRETH:** This is exactly the same
question.

**DR. MONTO:** How would I explain that we have a
different question?

**DR. HILDRETH:** Yeah. How would we explain
that?

DR. MONTO: Yes, I get it. I get that.

DR. FULLER: Dr. Monto, may I ask a question that’s not related to the phrasing, but a very important one to the question?

DR. MONTO: Yes, please, Dr. Fuller, and then we’ll try to go in order. It’s a lot easier to manage.

DR. FULLER: Thank you. Dr. Gruber, I definitely hope this does not happen, but what if there is some adverse event that appears, that is very broad, that this does not -- if we think the benefits outweigh the risk, but it turns out the risks are so high. How does this EUA get withdrawn? What will be the conditions to say that we can no longer do this?

DR. GRUBER: So as Dr. Fink had elaborated on in his introductory remarks, an EUA -- and he did say this last week, and I believe he said it today, too -- can be revoked. And there can be several reasons. So one could certainly be if we see that the risks outweigh the benefits of that product, then we can
revoke the EUA. So that is an -- but that’s -- right
now, we’re voting on the data.

We’re looking at benefit and risk based on the
data available to us and as we have presented them
today. And we, of course -- as was stated, we will
have continued follow up, active safety follow up, of
the recipients of this vaccine under an EUA. And if we
determine that the risks are no longer, well,
acceptable and that the risks outweigh the benefits,
then we can revoke the EUA, Dr. Fuller.

DR. FULLER: And FDA would do that?

DR. GRUBER: And the FDA would do that, yes.

DR. FULLER: Okay. Thank you. Thank you for
the clarification.

DR. GRUBER: Yeah.

DR. MONTO: Dr. Offit, let’s just go by
recognized -- individuals I recognize.

DR. OFFIT: Thank you. So yeah, I disagree
with Dr. Meissner. I think the question that’s being
asked us is do we have enough evidence in hand to say
that the benefits of this vaccine outweigh what, at the moment as far as severe safety issues, are theoretical risks. I think the answer to that question is clearly yes. I mean, the question is never when do you know everything? It’s when do you know enough?

You know, we have trials of 44,000 and 30,000. That’s as big as any general pediatric vaccine trial. The difference is length of follow up, so we don’t know whether or not it’s going to be effective six months from now or a year from now. But there are systems in place to know that. We don’t know whether or not it’s going to have a rare serious side effect, which is true of any medical product. But there are systems in place to know that. And frankly, given what we know so far about the height of the immune response, about what we have with T helper cell and cytotoxic T cell response and so forth, we can feel pretty comfortable that this vaccine is going to have a benefit that lasts for more than the three months or so that we’ve studied it.

I think it’s a pretty easy answer. You can’t
qualify things as being experimental because you could always say that about any medical product. I mean, when the HPV vaccine came out, we could say, “Well, we think that it’s okay for seven years because that’s all we have data for.” So I think the answer to this question, at least as far as I’m concerned -- I completely agree with Dr. Gans -- is clearly yes.

Thank you.

**DR. MONTO:** Dr. Cohn. And we’re going to be discussing this until 5:00 Eastern, and at that time, we’re going to put it to the vote because there’s also another chance to explain your vote afterwards. Dr. Gans? Dr. Cohn, excuse me. Go ahead.

**DR. COHN:** Ditto to what Dr. Offit just said. I completely agree that the question is the right question and the data clearly show that the benefits outweigh the risks.

**DR. MONTO:** Okay. Dr. Pergam.

**DR. PERGAM:** Thanks. I completely agree with Dr. Offit and Dr. Gans. I think the preponderance of
data is totally in support of moving this forward. I don’t see any value in changing the terminology of this particular voting question.

I also think this idea that the EUA process is going to change future vaccine trials, et cetera, feels a little bit strange to me. We’re talking about a pandemic, which is not very common, where we really need to move this forward. And there’s really an effort to get this done quickly. I don’t see as much of a risk in the long-term that this process is going to be used on a regular basis for other vaccine trials. So I think we need to focus on what’s at hand and focus on the question here, and I think there’s no doubt in my mind that the data is -- it looks like the benefits outweigh the risks from what I’ve seen.

DR. MONTO: Mr. Toubman.

MR. TOUBMAN: Yes. My camera’s not coming on, but can you hear me?

DR. MONTO: Yeah. We can hear you.

MR. TOUBMAN: So I’m fine with the question as
is because it says, “based on the totality of scientific evidence available,” meaning that’s what we have today. And based upon that, on balance, strong data particularly on severe disease, I think the balance supports it. I did have a concern though with — I’m glad there was discussion about whether to change the question or not, because I was troubled by the fact that FDA was weighing in again on us changing the question. And basically, we’ve been told this is an independent committee, and we want to be transparent.

If the Committee feels that a question should be changed, the Committee should change it. There doesn’t seem to be a willingness to trust the Committee’s decision, and the answer Dr. Gruber gave is, “Well, first, vote on my questions, and then after that, if it doesn’t pass, we can do a different question.” That in reality doesn’t work because almost nobody’s going to want to vote no to this question as written.
You deprive people the opportunity -- and this happened last time -- not to bring up the whole story. But with Pfizer there was strong feelings about including 16 and 17-year-olds. And because that was not presented as a separate question, which it should have been, people were sort of forced to have to make a choice. So I think the Committee really should be independent and decide for themselves whether the question is acceptable or not. In this case I think it’s fine.

DR. MONTO: Dr. Meissner.

DR. MEISSNER: I didn’t realize my hand was still up.

DR. MONTO: Okay. Well, then, thank you, unless you have some burning thing to say.

DR. MEISSNER: No, all I wanted to say, Arnold, is that I agree with what everyone has said, and I am in favor of yes on this question. My only point is I don’t want people to interpret this the same way they would a licensed vaccine. It is, as has been
stated, based on the available evidence, but that’s limited. But if everyone else is comfortable with this, I’m fully comfortable. Thank you.

DR. MONTO: And in reality, Cody, whatever we say, the media is going to interpret it in whatever way they want.

DR. MEISSNER: Yes.

DR. MONTO: Dr. Wharton?

DR. WHARTON: So the question as written seems to be aligned with how we think about EUAs. And based on the totality of scientific evidence available, I strongly support that the benefits of the vaccine outweigh its risk for use in individuals 18 years of age and older.

DR. MONTO: Okay. Dr. Neaton?

DR. NEATON: -- question. The answer is yes to the question. Thank you.

DR. MONTO: Okay. Well -- okay, then you don’t have to explain your vote afterwards.

DR. NEATON: All right.
DR. MONTO: Dr. Chatterjee and then finally Dr. Rubin. And then we will vote the question.

DR. CHATTERJEE: Thank you, Dr. Monto. I just wanted to follow up on several of the previous Committee members that commented on this, and I understand the difficulty that some people are having with the wording, perhaps. As scientists, we tend to be very precise in what we say, and we want it to be as to the point as possible. But I think what is not mentioned in the question -- and of course what we are all talking about -- is that we’re making this decision during a pandemic. And so there is this really unique circumstance that is forcing us, in some ways, to word the question in this way and to answer the question in this way. So I would say I’m comfortable with the way the question is written and willing to vote on it.

DR. MONTO: Thank you. And finally Dr. Rubin.

DR. RUBIN: Thank you. You can hear me?

DR. MONTO: Yes, we can and see you, too.

DR. RUBIN: Thanks. I’m glad to be
recognized. I just want to remember why we’re here. We’re here for two reasons that I can think of: to provide the FDA advice, and to see (audio skip) that they want. So I wouldn’t get so hung up on the question because they make the decision and we don’t.

And the second reason we’re here is to inspire confidence in the public that we’ve looked carefully at the data. And I think when we just -- when we worry about the details of the wording, I’m not sure that we’re helping people understand that what I almost certainly will be a very strong vote in favor is just a strong vote in favor.

DR. MONTO: Thank you, Dr. Rubin. It’s a delight to come to the end when I don’t see any hands raised, which was not the case last week. So now, let’s call the question. So we are going to be voting, and then after the vote, those who wish to explain the vote will have a chance to do so by raising their hands.

MS. HAYES: Thank you, Dr. Monto. Can
everybody hear me okay?

**DR. MONTO:** Yes, we can.

**MS. HAYES:** Okay. So our members and temporary voting members, as seen on the next slide, excluding the industry representative, will be voting in today’s meeting. And in regard to the voting process, Dr. Monto will read the question for the record, and afterwards, all members and temporary voting members will cast their vote by selecting one of the voting options. These include yes, no, or abstain. You will have two minutes to cast your vote after the question has been read.

Once all the votes have been placed, we will broadcast the results and read the individual votes aloud for the record. Please note that once you cast your vote you can change your vote within the two-minute timeframe. However, once the vote has closed, all votes will be considered final. Does anybody have any questions related to the voting process before we begin? Okay. I don’t see any questions. So Dr.
Monto, if you’d like to go ahead and read the question.

DR. MONTO: The question that we are voting on is, based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older?

MS. HAYES: Thank you. So members and temporary voting members, you have two minutes to go ahead and cast your vote.

DR. SAWYER: Arnold, this is Mark Sawyer. I want to point out that my vote says Pfizer-BioNTech, not Moderna.

UNIDENTIFIED MALE: Right. This is the wrong vote.

DR. MONTO: You are right. I was busy trying to find where the voting was.

MS. HAYES: Yes, we will be taking a revote. Just one moment.

DR. MONTO: We’ve got the right one up now.

MS. HAYES: Yes, I believe the question has
been updated, so we will restart the timer and clear
out the current results so we can take another revote.
We have 30 seconds remaining. Okay. Our two minutes
is up, so if we could go ahead and close the vote and
broadcast the results. And I will read the individual
votes aloud for the record.

So Dr. Cohn, we have a yes vote. Dr. Sawyer
voted yes. Dr. Rubin, yes. Dr. Kurilla abstained.
Dr. Perlman, yes; Dr. Schooley, yes; Dr. Gans, yes; Dr.
Lee, yes; Dr. Moore, yes; Dr. Chatterjee, yes; Dr.
Meissner, yes; Dr. Fuller, yes; Dr. Hildreth, yes; Dr.
Neaton, yes; Dr. Offit, yes; Dr. Wharton, yes; Dr. Kim,
yes; Dr. Pergam, yes; Dr. McInnes, yes; Dr. Monto, yes.
Mr. Toubman, yes. And that concludes the vote. It
looks like we have a favorable vote. So I will pass
the floor back to Dr. Monto. Thank you, everybody, for
putting in your votes today.

DR. MONTO: Thank you. Now, anybody who would
like to explain their vote should raise their hands.

Mr. Toubman is first.
MR. TOUBMAN: Thank you. I voted yes because the balance is strong. Last time (audio skip). Can you hear me?

DR. MONTO: We can.

MR. TOUBMAN: The balance is strong for approval, so that’s why I voted last time. I did recommend that we not grant EUA broadly, but rather limit it to priority groups to allow for further data to be collected, and since there is a limited supply anyway. And that would be to preserve the data we would get going forward. That was not accepted by folks. But we were assured that when Pfizer moves forward people who were not in priority groups would be maintained in the study. And that was really important to me.

I’m very concerned about Moderna’s proposal -- and it does sound like from the discussion -- I know FDA did not want to vote on that. I can see why. But it seemed like there was strong support for, if they’re going to unblind, they should do it on the basis of
when a group comes up in its priority and not unblind
everyone right away, which is what Moderna has
proposed. I think that would be really a disservice.

Finally, I did want to say thank you to the
FDA folks, though, because they put a tremendous amount
of work into this. I think Dr. Meissner said this at
the beginning of the meeting. In terms of very long
hours, reviewing the data, understanding this, working
with the sponsors, they’ve been under tremendous
pressure here and even they’ve been under improper
political pressure, even bullying and threats. And I
think they valiantly resisted that and showed that
science is going to prevail here. So a big debt of
gratitude to the hard-working FDA folks, Dr. Marks on
down. Thank you.

DR. MONTO: Thank you, Mr. Toubman. Dr.
Fuller, you’d like to explain your vote?

DR. FULLER: Yes, I would. Thank you. First
of all, I want to thank the FDA for the incredible work
they’ve done, and this Committee itself for the
transparency that went in today’s schedule and having more time. We’re in an unparallel crisis.

I did not think an EUA was the way to go, but since the train has left the station, I appreciate that Moderna has given us a very transparent and thorough study that even from the beginning seemed to be very well organized with getting people with underlying conditions, with monitoring activity throughout the study, with even including the serology and nasal swabs, which are not completely analyzed at the moment but which have great potential to look at important aspects. And then lastly the care for the study participants throughout, including a plan for monitoring adverse effects, as well as what to do with people who now may want to move from the placebo. So I appreciate the way that they’ve conducted a much more transparent and clean study.

And lastly, I know that now that we have vaccines available that we still have to use the preventions that are available such that we can keep
each other safe as we go through getting to the type of protection -- however long it lasts. So I want to thank FDA and all of you for helping with this discussion today, and that’s why I said yes. I didn’t feel that way last time. Thank you.

DR. MONTO: Thank you, Dr. Fuller. Dr. Kurilla and then for the final word, Dr. Hildreth.

DR. KURILLA: Yeah. Thank you, Arnold.

Camera not working again. I abstained because I’m very uncomfortable with the language. I think in the midst of a pandemic and with limited vaccine supply available, a blanket statement for individuals 18 years and older is just too broad. I’m not convinced that for all of those age groups the benefits do actually outweigh the risks.

And I would prefer to see it more targeted towards people at high risk of serious and life threatening COVID disease. And we have that -- they have that information, and we understand to a certain extent those high-risk groups. So it could be
Lastly, I would have preferred to have seen rather than an emergency use authorization route an expanded access program. I think it would have given us a lot more opportunities to continue to collect the data, and my concern about future vaccines was not on non-COVID vaccines but other COVID vaccine candidates that are in various stages of development. Thank you.

**DR. MONTO:** Dr. Hildreth.

**DR. HILDRETH:** Thank you, Dr. Monto. Sorry about the train. I just want to make the point that what a remarkable scientific achievement this is and say thanks to all the scientists present and past who contributed to this. To go from having a sequence of a virus in January to having two vaccines available in December is a remarkable achievement, and I just want to say that and congratulate all those who were involved. Thank you.

**DR. MONTO:** Thank you, Dr. Hildreth. You’ve echoed my feeling about what a remarkable achievement
has been reached here having the sequence less than a year ago. I just wanted to make one or two comments before closing. Our vote was even more overwhelming tonight than last week. I don’t think that anyone should interpret the difference in the vote being one way or another comparing the two vaccines that we have considered. Academics have a way of getting involved in details, and what we have done for the last eight or nine hours was to go over the details. And some people took the issues last week, especially those involving different age groups -- the 16- and 17-year-olds -- to drive the decision that they made, which clearly was made based on that issue and not on the overwhelming evidence for risk being less than benefit -- a clear benefit with these vaccines.

So I’d just like to close by thanking the Committee members, thanking FDA for giving us an agenda which allowed much more open discussion, which I think benefits all of us, including trying to advise FDA on some of these very tough issues that we are facing.
And congratulations to us all for achieving this emergency use authorization for a second vaccine, which along with other events will eventually and sooner, we hope, break the back of the pandemic. Now, I’d like to hand the floor over to Dr. Atreya to formally close the meeting.

MR. KAWCZYNISKI: Dr. Atreya, your phone’s muted.

DR. ATREYA: I’m sorry. Thank you all. Dr. Monto described my sentiments, and you all did a great job. And thank you for all your service and input. We greatly, greatly appreciate it. And then so I would formally close this meeting. This meeting is adjourned now. Thank you very much. Have good evening.

[WHEREAS MEETING ADJOURNED]