FDA VRBPAC Meeting Committee Discussion and Recommendations - Oct. 22nd

Docket No. FDA-2020-N-1898 for "Vaccines and Related Biological Products; Notice of Meeting; Establishment of a Public Docket; Request for Comments."

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Committee Discussion and Recommendations begins at 6:30:13 - https://youtu.be/1XTiL9rUpkg?t=23413
Committee Discussion and Recommendations begins on p. 298 - https://www.fda.gov/media/143982/download
Summary Minutes - https://www.fda.gov/media/143983/download
Meeting Roster - https://www.fda.gov/media/143532/download
Public Comments - https://beta.regulations.gov/document/FDA-2020-N-1898-0001/comment

FDA Guidance for Industry being discussed:
Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry - June 2020 - https://www.fda.gov/media/139638/download
Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry - October 2020 - https://www.fda.gov/media/142749/download

Questions addressed in the open discussion:
1) Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.

2) Please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine.

3) Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
a. Further evaluate safety, effectiveness and immune markers of protection
b. Evaluate the safety and effectiveness in specific populations

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https://youtu.be/1XTiL9rUpkg?t=23534
6:32:14
p. 300
DR. GRUBER:
So what we
would like for the committee to really focus on is we would like to hear are we on balance? Did we strike the right balance? On one side, we want a safe and effective vaccine available to the public as soon as possible, but on the other side we do realize that this cannot come at the cost of public health.
So what we would like for you to opine on is specifically are there areas or recommendations or data needs that are discussed in these guidance documents that you think as a committee are too strict or conversely are they not strict enough? Are there areas of broad disagreement in some of these guidance documents or is there broad agreement?

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6:34:13
p. 302
DR. GRUBER:
And we are concerned about the
risk that use of a vaccine under an EUA would interfere with long-term assessment of safety and efficacy in ongoing trials and potentially even jeopardize product approval in not only the first vaccine but maybe even follow-on vaccines.
And continued follow up of clinical trial
participants to further refine efficacy estimates to look at durational protection and the potential for enhanced disease and to obtain the required safety

follow up is essential and can't really only be successfully accomplished ideally with keeping these trials blinded. And that's why we're asking you to discuss this question if there are other considerations.

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6:42:08
p.308
MR. TOUBMAN:
I was concerned that the endpoints did not require serious disease, even moderate to serious disease, only some symptomatology. And the concern there is that we could have a vaccine that seems to do well meets the 50 percent test, and it's effective in avoiding mild cases but actually does very little to address what we really care about, which is serious disease and deaths.

https://youtu.be/1XTiL9rUpkg?t=24233
6:43:53
p. 309
MR. TOUBMAN:
But my question was, why the difference between the 50 and 60? Why is it not 60?

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6:44:07
p. 309
MR. TOUBMAN:
A median of two months to experience post -- the final regiment, the second dose if there's a second dose. And it was pointed out that means half the cases won't have been -- people won't have been inoculated for two months, that it'll be less than two months. And the explanation we were told that the document says that most of the adverse effects occur in the first six weeks. But they could be longer than that and we're talking about drugs based on untested, or I should say unused platforms that have never been the basis for vaccines.
So there could be adverse effects we don't know about. And so isn't two months a little short? And in finishing this question I would note that the

WHO has a three-month minimum test for their, what they call emergency use lifting.

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6:45:23
p. 310
DR. FINK:
So the
first question was about the primary efficacy endpoint being any disease versus being severe disease. You know, here we are really trying to strike a balance between getting information on the most clinically significant outcomes of COVID-19 and how a vaccine might be able to prevent those outcomes, versus being able to make an impact on the pandemic in as reasonable amount of time as possible based on good data.
And so, in trying to strike this balance and
also really having to acknowledge that the vaccine manufacturers are free to choose what they consider to be the most relevant primary endpoints for their vaccines. And then we evaluate whether the data supports that the vaccines are effective for that specific indication. And then other bodies, such as ACIP determine whether the vaccine should be used in certain situations. We felt that we could not mandate a specific primary endpoint, including a primary endpoint that focused on severe disease.
Now, that being said, when we do make our benefit/risk determination for NEUA or for licensure we do expect to have data to inform whether the vaccine is, or may be, effective against more severe disease.
We -- because more severe disease is going to be less common, then we will unlikely have in an analysis that used a less severe disease endpoint as the primary analysis. We will unlikely have, with the same degree of statistical rigor, evidence to determine effectiveness against more severe endpoints. But we do expect to have some, and we will use that evidence as one piece of information to inform our benefit/risk determination.
I'll also mention that there are multiple
examples of vaccines where the data do appear that the vaccines are most effective against more severe

disease, less so against less severe disease, and even less so against asymptomatic infection. So we took that experience into consideration as well.

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6:48:23
p. 312
DR. FINK:
To answer your second question about 50 percent versus 60 percent, I'd have to go back to Dr. Marshton's slides to remind myself of whether 60 percent was a success criterion that had been outlined for specific study or an assumption of vaccine efficacy that was used to calculate a sample size for that study. I think it might have been the latter. We, as I mentioned before, we make our recommendations based on what we think is an efficacy standard that would be needed to make an impact on the pandemic. And of course, we would not argue with any study that aims to go higher.

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6:49:07
p. 313
DR. FINK:
in terms of the two-month follow-up, we do recognize that other organizations and individuals including WHO have specified and advocated for a longer follow-up duration. Again, this was a consideration of balance in terms of having the amount of safety data that we thought was absolutely necessary to inform a benefit/risk consideration given what we know about vaccines and vaccine safety in general, and the goal of actually not withholding a vaccine that could make an impact. With the trials that are currently underway, we do acknowledge that some subjects will have been enrolled later.
Some subjects will not have quite two months of follow-up at the time an interim analysis to supporting the EUA might be conducted. But we are still talking about many thousands of vaccine recipients for which two months or more of safety and efficacy follow-up data would be expected to be

available.

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6:54:19
p. 316
DR. PERGAM:
My question is, I know that
enrollment has been difficult in high-risk groups,
particularly the racial minorities.
And there's no specification about including
the appropriate number in the EUA specifically that I
could find that suggest that it would be equal numbers
based on what the trials should look like. And I'm
concerned that if an EUA's put forward without adequate
enrollment in those particular racial minorities that,
that might be seen in a negative light. So I'm curious
how that was decided and is there any thought about
modifying that specifically?

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6:55:18
p. 318
DR. FINK:
Right. So, you know, we have not
ever had requirements for demographic composition of
data to support licensure of a vaccine and I think it
would be very difficult to outline such requirements
for EUA. Now, that being said I think we all
understand, and agree with, and support the importance
of having a diverse study population that is able to
provide safety and effectiveness data across the
demographic spectrum. That is the goal.
And so one way in which our regulatory action
can help to ensure that the vaccines being deployed are
safe and effective for the entire population for which
it is authorized is to make sure that the entire
population for which it is authorized actually has data
that supports the safety and effectiveness. So we will
be looking very closely at an EUA application to see
where the gaps are in terms of demographic
representation.
But I also have to caution that,
you know, we have had situations where, unfortunately,

you know, licensure applications have come in with less than desirable representation in certain, you know, say, racial or ethnic groups. That wouldn't a priori be a reason to restrict the vaccine from use in those groups. I just want to make that clear.

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6:58:12
p. 320
DR. NELSON:
we're
all anticipating that the initial application for EUA will have insufficient enrollment for some of these higher-risk groups or underrepresented groups. Does that mean when the EUA's authorized if there's not enough data for those groups they will be excluded from having access to that vaccine under the EUA?

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6:58:54
p. 320
DR. FINK:
as I mentioned in response to the previous question, we will look carefully at the demographic representation for safety and effectiveness data, and we'll approve or authorize the vaccine for those populations for which the data support safety and effectiveness and favorable benefit/risk. There may be circumstances in which demographic representation is less than we would like, or not large enough to make firm conclusions. But those types of gaps would not necessarily in and of themselves result in a restriction.
We would have to think about whether it makes sense from a scientific basis to be concerned that there is some difference based on differences in demography to result in such a restriction. The most common example that I can think of would be age. We do not automatically assume that if the vaccine works for one age group that it will necessarily work for another.
And so, for example, if we had very limited data on safety or effectiveness in elderly individuals,

that would cause us concern and we would have to consider whether the data really did support authorization or licensure of the vaccine for use in an elderly population.

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7:00:53
p. 322
DR. NELSON:
with the potential for delays in bringing vaccines for full licensure, some of the excluded groups who aren't part of the initial EUA might have to wait even longer. And I think if you look at what some of the strategies for deployment, there may be disconnects between the initial intent of deploying the critical infrastructure individuals and higher risk patients where we may not have the sufficient benefit of data for both safety and efficacy. So you see the dilemma that has been presented and outlined by our public testimony earlier today, that there is great concern about being able to acquire that data in these specific settings. Thank you.

https://youtu.be/1XTiL9rUpkg?t=25296
7:01:36
p. 322
DR. FINK:
No, I couldn't agree with you more.
We fret about that constantly. And so that
[not included in official transcript - “is why we are seeking your input on all three of these questions that we have out for discussion.”]

https://youtu.be/1XTiL9rUpkg?t=25382
7:03:02
p. 323
DR. ALTMAN-GANS:
in all of your safety data
I really don't see how the uniqueness of this virus and some of the components of its immune responses, not so much for immunogenicity of a vaccine but for safety reasons in terms of the immune and thrombotic events. I see none of that in, sort of, the FDA thinking in terms of vaccine safety, which actually may be markers

before the clinical disease. And waiting for those clinically is maybe something we can't afford to do with this particular virus.

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7:03:41
p. 324
DR. FINK:
So what you're describing, these concerns that are, you know, they're theoretical but they're certainly well-founded theoretical concerns, we are interested in them. We mentioned enhanced respiratory disease in our guidance as an example of a type of immune-mediated process chiefly because it's been described with another respiratory virus vaccine, RSV in the 1960s, and there were some animal data with SARS-1 vaccine candidates that raised that concern.
So I don't want the committee to come away with the impression that we're thinking of enhanced respiratory disease as the end-all-be-all of these types of concerns. We are concerned about phenomena that might manifest similar to MIS and other immune-mediated processes. And of course, we will be examining adverse event data that comes in with the safety follow up looking specifically at events that might be signals for these types of phenomena.

https://youtu.be/1XTiL9rUpkg?t=25504
7:05:04
p. 325
DR. MONTO:
have you thought about changing the guidance to enhanced disease instead of enhanced respiratory disease?

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7:05:16
p. 325
DR. FINK:
That is certainly food for thought. But I do want to make clear that we are thinking about it.

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7:09:03
p. 327
DR. HOLMES:
one of the questions that's very
important to ask is, can you prevent infection as well
as a treatment for the disease?

https://youtu.be/1XTiL9rUpkg?t=25751
7:09:11
p. 327
DR. FINK:
Yeah. I couldn't agree with you
more. That is a very important measure to evaluate and
of course sterilizing immunity is the gold standard of
protection but of course not always achievable. In our
June 2020 guidance, we did make a recommendation that
prevention of infection should be evaluated, if not as
a primary endpoint then as a secondary endpoint.
And that endpoint could be evaluated using
either serologic methods similar to what you described.
Not necessarily in the saliva, but that would be an
option, or through periodic sampling using virologic
methods. Although, those would have to be frequent
enough so as not to miss cases due to only transient
shedding. So we do agree with you that evaluation of
prevention of infection is important, we have
recommended that studies do that.

https://youtu.be/1XTiL9rUpkg?t=25818
7:10:18
p. 328
DR. HOLMES:
But I don't think that it would
be very practical to do that with serology to get a lot
of volunteers to take a lot of blood tests over time.
Whereas the saliva test which was just recently
validated I believe would perhaps be more accessible.

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7:11:18
p. 329
DR. WENTWORTH:
I

had a question related to this two-month pre-market follow up again. So I think, you know, some of your rationale, some of the rationale presented is quite strong. But here we're dealing with some, you know, generic recommendation and some very new platforms, such as mRNA as a platform. And that's very different than most of the things that have been given to people at large, in large amounts, being mostly either just for combat proteins or purified proteins from viruses, et cetera.
And so I guess I wonder, did you consider a longer time frame depending on, you know, the platform itself? Here you're talking about a spike glycoprotein that interacts with a receptor that has physiologic, you know, responses that it controls, and you don't exactly know where all these lipid nanoparticles are going to end up in the host. So I guess I was just wondering, is there any idea to do a longer pre-market follow up for those, kind of, more unique platforms that we have less of an understanding of?

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7:12:30
p. 330
DR. FINK:
Right. So first of all just to clarify, when you talk about pre-market follow up, we're really talking about six months. The two-month benchmark is to support EUA, which, you know, is a somewhat different benefit/risk calculation although not that different when you're talking about millions of people, admittedly. So, you know, we regulate vaccines of all different technologies as Dr. Gruber explained in her introductory comments. We have the same set of regulations that apply to all vaccines independent of what the platform technology is. Again, we did consider novelty of platform among all of the variables in our considerations but ultimately came out with our guidance as a way to strike a balance. If the committee has strong feelings or recommendations about how these considerations should be handled differently, then we would certainly want to hear that.

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7:14:09
p. 331
DR. HILDRETH SR:
I
just want to make two quick points with Dr. Fink if I may. The first is that since severe disease and -- that occur primarily among minorities with this virus, if we put a vaccine out there that does not address that issue it's just going to perpetuate the perception that this -- that that population or that segment of our population does not matter much in dealing with this challenge. So I would just ask for consideration be given to making sure that whatever we do we have a vaccine that does address severe disease.
And I'd like to make -- the other point that you said you cannot mandate what the drug companies might set as their primary endpoints, if I'm not mistaken the taxpayers of the United States of America are paying a -- the tab for this, so maybe you might have more authority to mandate than you might think. I'm just -- want to put that out there. So I just want to make that point.

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7:15:20
p. 332
DR. MONTO:
I want to move the committee to the discussion items now. And the -- I want you to think about our conclusions because we are being asked to summarize our conclusions and I think we can lump together one and two and come up with a single set of conclusions for both. But let's look at number one first. Please discuss FDA's approach to safety and effectiveness data as outlined in the guidance documents, which means both EUA and full licensure.

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7:17:36
p. 334
DR. FINK:

Thank you very much for
pointing that out. I tried to touch on that when I was
responding to one of the questions, I think, about
demographic representation and what an -- what
population an authorized use might include. And, of
course, I think it's helpful to clarify that FDA does
not have the authority to mandate demographic
representation in clinical trials. We're required to
report to Congress about demographic representation in
clinical trials that support licensure of a product,
but we can't mandate that.
What we can do is make sure that the product
labeling accurately reflects the available data so that
recommending bodies such as ACIP, and also individual
healthcare providers, and patients, are able to see
whether the data applies to them and to make decisions,
whether it's for use in individual or use in a large
population, about whether the data would support that
use.

https://youtu.be/1XTiL9rUpkg?t=26329
7:18:49
p. 335
DR. MONTO:
Thank you. And you can -- we can
-- you can only review and make decisions about what is
presented to you and that's why we really need to have
a discussion about the guidance documents because
that's what we have to go on. And we're being asked to
look at them and to see if we agree with the approaches
in the guidance document, and what we think about them
in terms of their implementation. So let's get back to
the guidance documents

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7:19:37
p. 335
DR. NOTARANGELO: Thank you. So I would like
to echo what others have already mentioned. And I am
specifically now looking at the document. I have
problems with the standardization of efficacy. I --
first of all, I do appreciate that it's very important
to standardize efficacy across multiple trials,

multiple platforms. But the problem is that these efficacy measures that are included in the document, they have two problems. First of all, they really are biased (inaudible) with mild disease. And that is a concern that I do share with Dr. Holmes actually. Her consideration that much more emphasis should have been put on actual infection and perhaps on severe disease at the same time. Mild disease may not mean very much.

The other problem with those efficacy measures is that most of them are really subjective. There are very, very few that can be actually objective measures. And I think that's a major concern. I mean, we're relying basically upon reporting from the subjects without any objective validation of what they're reporting. I'm really concerned about this. And this applies to the EUA and to licensure, in my mind.

A few other comments, I agree completely with Dr. Meissner. I think at this point based on what we've been presented I am very concerned about extending the, you know, immuno-bridging from adults to children. I think children at this point should not be considered for use of this vaccine until there is sufficient evidence, and what we've been presented today does not provide that.

And finally, I think given that we are dealing with new platforms, I don't really understand the reason why the manufacturing facilities are not inspected. I think that is something that could be done. It could be done even ahead of time. I think it would provide some additional, you know, trust into the process.

Finally, you know I understand that we, you know, the FDA cannot mandate demographic breakdown. But I do agree with Dr. Hildreth that if we do not have sufficient evidence that the minorities, and in particular our black population are included in this, you know, trial data, their trust will diminish even farther.
And the net effect will be that perhaps the

white population might be protected and we will only see cases of severe COVID among the black, which would be a total disaster from a, you know, social standpoint. So I don't know what can be done but something should be done to facilitate the inclusion of a vulnerable population, in particular the black population in -- at this point. Thank you.

https://youtu.be/1XTiL9rUpkg?t=26614
7:23:34
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DR. CHATTERJEE:
as we deliberate on what
data are needed to ensure, first of all, safety.
I think from the public hearing comments as
well as the comments that were provided by the Reagan-Udall Foundation folks, it's very clear that the public has significant concerns about safety. And so I think, for me at least, the most important thing is to make sure that whatever products are put on the market under whatever mechanism, whether it's a BLA or an EUA, that first and foremost these are safe. And then you get to the effectiveness piece of it which I think is also critically important, not less so necessarily, but I prioritize those two things, in my mind anyway, in that fashion.

And so the last thing I will say is with
regard to the vulnerable populations around which there has been a fair amount of discussion as well, I do believe that it is again critically important, whether the agency has the ability to mandate it or not, it definitely has the ability to encourage the manufacturers and ask them to include these populations that are at the highest risk of poor outcomes from this infection. So as we consider what's going to happen with these products, I think it would be very important for us to keep that last piece in mind.

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7:25:26
p. 340
DR. ALTMAN-GANS:

Thank you. I'm not going to
reiterate things that have already been said about the
efficacy and certain study populations of all which I
agree with.

My points are that in terms of number one
I really feel like they haven't gone far enough in
terms of the safety outlines, as people have indicated
efficacy, as well. We really need to be thinking about
this differently and we really need to be guiding what
we do in terms of our safety. And some of the points
I've brought up which I didn't feel like were fully
answered in terms of some of the ways in which we know
that it affects people and they're missing this in
their safety data.
So nobody's collecting, as far as I can tell,
anything about immunogenicity data and they're waiting
for people to get clinical outcomes that would bring
them to presentation. We have no immune markers, not
thrombotic markers, which again, may actually be
biomarkers that precede some of this and could prevent
people from having to become ill before we actually see
an adverse event from a biologic. So that is a safety
outcome that I think should be part of this.

The other part of this in terms of one, and
we've already heard, which is around the EUA and the
timeframe. And I think the public, as has been
suggested, is probably not going to have an appetite
for anything short of a vigorous process which we're
used to seeing, is that we really have to have again
differing approaches to the way in which we use our
databases. It's not enough to do this kind of passive
reporting that we have.
This is not going to be enough for this
particular vaccine and the way in which we see the
scrutiny. We don't have the time, we can't wait, and
so we're really not utilizing our electronic
capabilities at this point. This is going to feed into
number three as well. And so I think that it's a
really hugely missed opportunity that we're not going
to be able to turn around and do.

And only last point I will bring up is that some of these vaccine platforms may be more effective in certain populations. And unless we have an adaptive way of looking at those and looking across we don't want to bring -- we should have the ability to look at these vaccines in a more real-time fashion in terms of what we approve for what population. If one is better in the elderly versus some of our under-represented individuals, we should have that ability and we're not situated to do that. And this needs to be done. We need to look at these differently than we have looked at other vaccines since so many are being brought to the market. And the only --

The only last thing I did want to say is I think we shouldn't disclude the immune-bridging for children. I understand that there's real concerns about different safety issues. We should absolutely have those involved, but, you know, that is something that has been done for other vaccines and it isn't something that we should completely, I feel, take off the table.

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7:28:58
p. 343
DR. KURILLA:
With regard to the 50 percent efficacy, I -- to me that's a minimum threshold. But I think the issue here is that it's not a threshold for -- it shouldn't be the minimum for everything. And so I have some concerns about the utility of a 50 percent reduction in symptomatic disease when we don't really have any evidence that these vaccines are going to induce sterilizing immunity.

And so the idea for healthcare workers and other high-risk individuals, long term care facility staff, that sort of thing, something that would reduce their risk of infection -- that would take them nearly from a mild infection to potentially an asymptomatic infection where they still might be infectious doesn't

seem like it's something worthy of an EUA.

Now, on the
other hand, a 50 percent reduction in the progression
in high-risk groups to serious disease, you know, that
is actually very -- quite significant.
And so that is something that to me would be
EUA-able. So, you know, for the first responders and
primary healthcare workers and LTCF staff, the minimum
has to be much, much higher in terms of having a
general overall public health impact. And so, you
know, I think -- it can't just be whatever group hits
the target that's what gets EUA'd.

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7:30:38
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DR. MONTO:
Dr. Kurilla, how do you do that
from a feasibility standpoint? Having flexible
outcomes for different -- flexible efficacy for
different outcomes?

https://youtu.be/1XTiL9rUpkg?t=27053
7:30:53
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DR. KURILLA:
so
they have their protocol, they have their trial design
but when they do the -- it's going to be these interim
readouts and you're going to get some assessment of
efficacy. Now, if they come out and say that, you
know, normal, healthy adults we only saw 55 percent
reduction in COVID, I -- that just doesn't strike me as
something that I would want to EUA because I don't
think it's going to have that significant of a public
health impact.
Coupled with the fact that people get the
vaccine and that they may in fact be unaware -- so
almost half the people would be not protected. They
may not -- and they may still get mild or asymptomatic
disease anyway regardless of whether they've been
vaccinated or not, no idea, unaware of their infectious

state. Now, a 50 percent reduction in a high-risk group that goes on to more serious disease, that, I think is something that is -- that merits at least some consideration for an EUA. It would target those groups that are at a much higher risk.

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7:32:03
p. 345
DR. KRAUSE:
Yeah. Thanks, Dr. Monto. I just wanted to make a comment because it's very difficult when thinking about different possible endpoints to think about what they mean. And of course, this also has to be thought about in terms of the frequency of each of these possible endpoints. So if the endpoint of the trials is severe disease, the trials may need to be almost ten times as big. And those trials would be infeasible, and we would never get a vaccine.
If the endpoints are infection, that can, with some additional work, be a feasible endpoint. But the science is not there to do that right now. So what we have looked at is the fact that a vaccine that is, in general, effective against mild disease, there is -- simply does not exist an example in vaccinology of vaccines that are effective against mild disease that are not more effective against severe disease. And so a 50 percent effective vaccine against mild disease is very likely to be greater than 50 percent effective against severe disease. And --

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7:33:13
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DR. KURILLA:
Except Phil, many of the groups at risk for severe disease don't respond well to vaccines in the first place.

https://youtu.be/1XTiL9rUpkg?t=27207
7:33:27
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DR. KRAUSE:

And so that is the rationale.
Now, the 30 percent lower bound is critical as well.
And if you want to have a 30 percent lower bound for severe disease, that also makes the trial much, much bigger. But the trouble is, is that when you're dealing with many different vaccines, if you don't have stringent statistical criteria for success there's a very high risk that a vaccine that has marginal benefit, or possibly even no benefit, will meet the criteria just by chance. Because we're not talking about just evaluating a single vaccine, we're talking about evaluating multiple vaccines.
So if you're going to do evaluations of vaccines you have to look at what is feasible and what will give you the information that you need.

And don't
forget that these trials are intended to continue well beyond whatever the timing of these interim analyses would be and will continue to gather information about impact on severe disease. And so they're designed to ultimately get the information that is needed.

And so one of the questions that you are being asked, of course, as a committee member, is what is the level that makes you comfortable with an EUA, or what is the level that makes you comfortable with broader deployment of a vaccine?

And so that is, of course, a
balance between looking at people's rights to take something where it's determined that the benefit might exceed the risk, while also making sure that we don't interfere with the public health good, the public good associated with continuing to evaluate that vaccine and other vaccines, while also making sure that people are not taking vaccines that might actually harm them.

And so it is a difficult balance to figure out
exactly where that is. And it may be -- as you know Marion did put forward the expanded access regulations as one approach that could be used. One could potentially contemplate an EUA for a rather limited

population. But of course one doesn't want -- if there's a vaccine that appears to have high efficacy or appears to be capable of saving lives, one doesn't want to stop that vaccine if there's a significant chance that it will save lives because that's part of the public health calculus as well. So I will stop there.

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7:35:55
p. 349
DR. MONTO:
I think
we're going to have to move on. We've got a lot of people who want to make comments. I think what we have to do is keep focusing on EUAs versus BLAs, formal licensure, and not really try to talk about sterilizing immunity or other things which are not part of standard vaccine licensure.

Most of our vaccines are licensed to prevent laboratory-confirmed disease and those diseases are different depending on what they are. And we rarely get into looking at a definition of serious disease and as Dr. Krause said, things that prevent infection and laboratory-confirmed infection typically prevent serious disease and maybe do a better job at that.

https://youtu.be/1XTiL9rUpkg?t=27459
7:37:39
p. 350
DR. COHN:
I am actually less concerned
about, for example, adverse events in the 30,000 participants in the clinical trial after the two-month follow up as I am potentially about more rare adverse events. And anything in terms of prolonging or thinking about waiting longer isn't, from an EUA perspective, won't change that. But this is why we have our safety surveillance post-authorization needs to be so strong and effective so that we do identify potentially more rare adverse events than you would identify in a trial with 30,000 individuals.

The second point I want to make is that I do worry a little bit that the VE estimate for mild disease may be overestimated when we're just looking at the first two months after vaccination and that we may have a lower VE estimate, for example, if we looked at the data after four or six months just because of waning immunity.
Very rarely do we look at VE so shortly after completing the series. And so I don't think it's a factor that would lean me towards not agreeing with the 50 percent. But I do think it could be a potential communication issue if it hovers on that 50 percent point estimate after two months and then it falls much lower when we actually look at the data for BLA.

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7:39:20
p. 351
DR. MONTO:
Which is why we have to continue to keep the randomized design. Right?

https://youtu.be/1XTiL9rUpkg?t=27612
7:40:12
p. 352
DR. OFFIT:
So just, it is disappointing, I think, that given that this is a vaccine that's being paid for by the public -- I mean BARDA is public money -- that the FDA can't direct this vaccine to make sure that we are testing it in groups like those who are at greatest risk, the various racial or ethnic backgrounds, health problems or age. That said, I mean, I'm on the NIH Active Group, which was put together months ago by Dr. Collins. And on that group were members of the industry, Pfizer, Moderna, Merck, and those people were on that working group. And so when we -- when Larry Corey, who headed the clinical trials subcommittee, was putting together how he wanted these trials to be done, this was key.
I mean, we did not want this to be a study of, you know, healthy young white people. We wanted this to be a study that represented the American public at

greatest risk. And my sense from those discussions is that is exactly what they're going to do. So I don't -- I understand Dr. Hildreth's concern but I think when this is -- plays out that we're going to find out that these are represented, groups. And in fact, one of the company's actually slowed recruitment because they weren't getting enough in the way of minorities. So I don't think in the end this is going to be a problem, but we'll see. Thank you.

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7:41:45
p. 354
DR. ANNUNZIATO:
Okay. I just wanted to make a point that, you know, vaccine researchers and developers, manufacturers, public health entities, and so many others have really collaborated in a very focused way in order to try to deliver safe and effective vaccines in this very short period of time after the emergence of this virus. And I think, what I've heard today at least, is that there's broad concern that the speed of this response has been at the expense of careful scientific methods and we need to continue to work to address this perception.
That being said, I myself find that the thoughtful consideration and the clear guidance that the Agency's provided in these two guidance documents on the regulatory requirements for full licensure as well as for EUA will in fact help us as manufacturers and sponsors develop COVID-19 vaccines that will be held to the highest standards as we've heard today.
And so I, in fact, want to commend, you know, our colleagues that we've heard from today from the FDA for their, you know, timely and careful consideration, understanding -- as it's been said -- we're trying to fly and build this plane at the same time, and that nothing will be perfect. I do think that these guidance have struck a key balance and should be supported.

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7:43:42

p. 355
MR. TOUBMAN:
I also appreciate the difficult
balancing that has to go on here and all the work that folks at the FDA have (audio skip). I'm coming, obviously, from the consumer rep's point of view, no technical background, so all I have really is, you know, I try to follow up on what's been going on and common sense. But also, I'm very affected by the public perception because in this particular case public trust equals success. Lack of trust means no success. That seems pretty clear. And where that leads me to is a conclusion that EUA probably should not be used here.
And I say that because, first, start with the fact that EUA is almost always used, I think there's one exception, for people who are sick and you're basically putting something which is not fully tested but they are ill and so it makes sense you have to do something. And the balance changes there. Vaccines is a different story. But almost everybody's going to be injected is going to be healthy at the time they get the injection, so I think that has to be factored in anyway.

But on top of that, we have serious vaccine hesitancy. And now we have, as the speakers made clear, and really I greatly -- I think we all appreciated the Reagan-Udall Foundation data and information because basically what we're hearing is that the perception is that this is the speed and it's a result of political pressure and that's what it's really about. It's not about the science. It’s not true. But that is the perception.
And so anything that sounds like emergency use authorization, you know, it sounds like it's being done rushed and it's not the full review so even if it were -- even if EUA standards were similar to full licensure it doesn't sound good to the public. And again, what it sounds like matters. But here there is a difference and that -- and there are several differences.

But one

is that the primary one is duration, is that it would be median two months. And whereas -- and I understand that full licensure is probably like six months. So there really -- that duration makes a difference in terms of both safety and efficacy.

And you have to note for that -- for the second question, sorry I'm jumping ahead. But the problem of people bailing from the test if you go -- if EUA's granted what happens is people in the placebo, you know, they move towards getting this thing anyway.

So those are a lot of problems with an EUA in this particular situation and that's before we get to the problem of likely poor participation by people of color in some of the studies. Although Moderna, it sounds like they've done a great job there.

I think that what Corey said it really sums it up for me, which is there's only one chance to, you know, to do this and do it right. If we do it wrong, then we're done for. It'll be years because the -- there's already a serious problem of lack of trust. The trust will become so severe at that point that we won't be able to dig out of it.

So given all of this and that public (audio skip) -- sorry. I was muted for a second there. I would recommend that we not do EUA here but if we're going to do it, I would suggest the following: That it be for a longer period. Not two months, maybe three or four months.

And two other things, if we are told that the primary endpoint can't be determined, and I'm surprised by that, I agree with Dr. Hildreth that looks worth looking at if the taxpayers are paying we maybe should be able to identify the primary endpoint. But in any event, it could the basis for EUA. If you're going to get EUA then the primary endpoint has to be something more serious in terms of serious disease.

And lastly, again, if we can't determine who

are the demographics of who's actually in the study we could say if it turns out that the demographics were not good then we're not going to grant EUA because of the risk. Whereas, if a company like Moderna, I guess, has really good participation that's representative that might be a reason if we're going to approve the EUA. But I would be very, very reluctant to do it under all of these circumstances, and particularly the public's hesitancy over this particular project. Thank you.

https://youtu.be/1XTiL9rUpkg?t=28094
7:48:14
p. 359
DR. MONTO:
maybe you could comment about the term EUA. Is there anything else it could be called?

Thinking back to other issues. And we also heard about longer than two months. Seems to me that if we answer positively, we can figure out how to continue the randomization. It doesn't really matter that much whether it's two months or four months.

https://youtu.be/1XTiL9rUpkg?t=28129
7:48:49
p. 360
DR. KRAUSE:
Yes, sir. I am. So my hand was up from before. I took it down now. But -- so, you know, we're obviously working within the framework of the regulations that we have. And so the emergency use authorization is one of the things that we can do, and expanded access is one of the things that we can to and BLA is one of the things that we can do.

One of the problems with the Emergency Use Authorization is that it's positioned in this way that is on the one hand close to BLA where we would like to have fairly high standards for it, and yet the EUA also does, in fact, represent an investigational product. It hasn't yet met the standards for licensure.

And you've heard some
of the data differences which include follow up.
But I don't want you to underestimate the
importance of the FDA review that goes along with the
BLA too. Because under BLA the FDA has actually
carefully reviewed essentially every single person
who's been in those trials and looked at what happened
to them, and has carefully looked at the manufacturing
process, and all the ways in which the manufacturing
process is controlled to make sure that this product
can be consistently made. And so although, if there
were an EUA the standards would be very high, as you've
heard, there is no way that they could be as high as
they would be for a BLA.

https://youtu.be/1XTiL9rUpkg?t=28213
7:50:13
p. 361
DR. MONTO:
And it is possible that something
which is -- a product which is given an EUA may not
receive a BLA because they can't meet those standards.

https://youtu.be/1XTiL9rUpkg?t=28223
7:50:23
p. 361
DR. KRAUSE:
Well, the hope would be that if
it got an EUA because it had at least the clinical data
that would make it likely to meet the BLA standards
initially that it would receive BLA. But of course,
it's conceivable with additional follow up, or with the
active safety follow up that FDA is also requesting
during a period of an EUA, that something would be
uncovered about that product which would make one not
want to license it.

And that's why the EUA product is investigational. It's not a guarantee of a BLA. And yet we would hope that products that are made available under EUA would subsequently qualify for BLA.

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7:51:06
p. 362
DR. MONTO:
And as you plan any issuance of an EUA will also have a committee review.

https://youtu.be/1XTiL9rUpkg?t=28276
7:51:16
p. 362
DR. KRAUSE:
That is absolutely correct. And that's in the guidance and we've heard both Dr. Hahn and Dr. Marks commit to that as well.

https://youtu.be/1XTiL9rUpkg?t=28285
7:51:25
p. 362
DR. MONTO:
So that we'll have this second chance to go over the specifics. Once we agree to the principals that have been put forward today in the guidance.

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7:51:37
p. 362
DR. KRAUSE:
That is indeed correct.

https://youtu.be/1XTiL9rUpkg?t=28310
7:51:50
p. 362
DR. PERLMAN:
Yeah. I just want to add to the idea that we should -- that we might want to prolong the two months to a few more months for a few reasons. First, from what we know about common coronaviruses and
immune responses we know that at two months is probably
a good immune response and that it wanes between six
and twelve months. There's plenty of illustrations of
reinfection. Whether vaccine's going to be the same,
of course, we don't know.
But as you have waning vaccines you might have
more chances to have any adverse -- not adverse
effects, but rather vaccine problems -- vaccine-related
problems that wouldn't be seen at the two-month mark.
In a way, two months would pick up a lot of the early
adverse events, but I think it's a continuum. We

certainly know the measles vaccine wasn't picked up as a problem until it killed one and took two to three years.
And we're not going to go that long, so there's a continuum and it's kind of a -- to me, in my mind, it's an arbitrary point of where you do things weighing everything together. But if you do a few more months and if this behaves like the responses to the common cold coronaviruses, we might have a chance to pick up these vaccine-related problems that we might not see at two months.

https://youtu.be/1XTiL9rUpkg?t=28386
7:53:06
p. 364
DR. MONTO:
Well, that's going to be followed if we keep the randomized trials going.

https://youtu.be/1XTiL9rUpkg?t=28406
7:53:26
p. 364
DR. MONTO:
So before we go on to number two, which again is related I just want to summarize what I've heard. And that is, there is some concern about the period of two months as being somewhat arbitrary, but recognition that the study will still be going on if randomization can be continued at least in a large subset of those that are being studied or receive the EUA.

That we want to be sure that minorities are represented and then, and this is a little bit outside the scope -- concern about immuno-bridging to children, that there's only one trial that goes down to age 12. And because of issues of immune response, et cetera, and MIS-C there is concern that it may be an inappropriate to use standard bridging guidelines.

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7:54:36
p. 365

DR. MONTO:
Saying that, let's go ahead and try to talk about the very thorny issue of continued blinding of Phase 3 clinical trials if an EUA has been issued. I know that in one of the letters we received from one of the manufacturers it said that anybody who is eligible to receive the vaccine under EUA who has been in the clinical trial will, for ethical reasons, be offered -- and in the placebo group, will be offered vaccine which breaks the blind.

Let's have a more general discussion of this issue because one of the reasons why we would feel comfortable with getting the EUA issued after two months is that there will be continued follow up to see if there's waning of immunity, to see if there are side effects over a longer period of time. So I'd like some contributions about -- clever ideas about how to continue observations even though an EUA is issued. And I think there may be issues also about how much vaccine is available at the issuance of the EUA, and the fact that certain population groups might be included in the EUA, and other groups would still not be able to receive vaccine under the EUA and therefore could be continued in the randomized trials.

https://youtu.be/1XTiL9rUpkg?t=28616
7:56:56
p. 366
DR. MEISSNER:
I just wanted to make one comment about why the two-month interval I think was selected in terms of follow up for the vaccine. It's a tie-on to the last discussion. But most adverse reactions occur within the first six weeks following administration of the vaccine.
For example, Guillain-Barre syndrome when that's followed an influenza vaccine to have occurred within that four to six-week window. So I think that's the basis for selecting eight weeks. I agree, it's short for vaccines with a new platform, but I don't think it's a completely random selection. So that was just a tie-on.

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7:58:02
p. 367
DR. MEISSNER:
Thank you, Dr. Monto. I -- and then the question I have on unblinding is, was this addressed -- this issue addressed in the informed consent that everyone must have signed? I can't imagine that the informed consent didn't address the issue of what would happen if there was a conclusion. And so I think, isn't -- that should be stated.

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7:58:29
p. 367
DR. MONTO:
Very interesting point. Most informed consent say that people can withdraw at any time anyway. So is there anybody who can respond to that?

https://youtu.be/1XTiL9rUpkg?t=28728
7:58:48
p. 368
DR. KRAUSE:
So in general in these
trials, there's not built into the trial protocol,
cross-over. And so there has not been any promise to
the people in the trial that they will be eligible to
receive a vaccine when it becomes available. And, of
course, if they were to become eligible the question
would be, when? If the EUA came about as a result of
an interim analysis, would that be the time at which
one would do that, or would one wait until the trial
had actually finished?
The vaccine then might be -- one had more
data, and the vaccine might be available for licensure.
But to answer your question, there isn't a priori any
promise to the people in the trial that they will
receive that. And so presumably that kind of a promise
was not required to induce, obviously, the volunteers
who I think generally joined the trials out of a sense
of altruism and a desire to help. But -- so to
continue them on placebo wouldn't break a deal.

I'll make one other point and that is that
vaccine recipients -- placebo recipients otherwise
likely wouldn't be the first in line to get a vaccine.

Normally you would think about the first in line even as a vaccine became available would be those who are at greatest risk, or perhaps members of under-represented minority groups and so forth. And if anything, the average trial recipient might actually be at a lower priority than certain other people who might be in line to get a vaccine.

And then, of course, third, not prioritizing placebo recipients to get vaccine once it became available, even if a vaccine is 100 percent effective doesn't put them at enormous risk. Obviously, everybody is at some risk, but everybody also has other ways to protect themselves. And even if these people were kept in the trial for some additional period of time, many of them will surely get the vaccine long before other people do just because of the likely availability and the roll-out of vaccine.

And in fact, we heard this morning in one of the presentations that many people will want to wait at least six months before a vaccine is made available before they would take it anyway. And so that's sort of -- is an argument also that there may not be a clear obligation to people who are in the trial to give them a vaccine even if they were originally randomized placebo once there was an EUA.

So I'm sort of summarizing these. These are arguments that I've heard.
I'm not myself an ethicist but I have heard discussions about this as --on this general topic and these are some of the considerations that are brought forward in thinking about this, make the argument that there wouldn't necessarily be a strong reason why one had to do it. So for those who say there's an ethical reason, I think that that's perhaps overstating the case.

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8:01:55
p. 370

DR. MONTO:
While you are there, Dr. Krause,
can I ask you whether an EUA could be issued for
healthcare workers or first responders, or groups like
that? That's usually something that's handled by ACIP.

https://youtu.be/1XTiL9rUpkg?t=28935
8:02:15
p. 371
DR. KRAUSE:
So I think we would have to
figure that out. It's difficult. One could
contemplate a very limited EUA based on a perception of
what the risk was, for instance. Because EUA is
authorized based on a benefit/risk calculation and so
if, when we were to say well, we want to make this
vaccine available to people who are in the highest risk
group, one could try to cut it that way. I think it
might be harder to do it based on other factors than
risk. Although, you know, that's not something that
we've in the past done.
There's only been one vaccine EUA in history
and so exactly what we are able to do there is unclear.
Of course, on alternative might be to -- if vaccines
become available early to use them under expanded --
not become available, sorry. If an interim analysis
suggests efficacy, one could start with an expanded
access, and then as one gathered data then perhaps move
to an EUA. But of course, there's some complexities there also. Under expanded access one surely would have very high degree of control over who could get the vaccine.

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8:04:04
p. 372
DR. PERGAM:
Yeah, thanks. I wanted just to
emphasize one of the points that you made, Arnold, is that I'm not sure how much vaccine's going to be available. And so this is really going to be part of the EUA thought process is, making an EUA available does not necessarily indicate that we're going to have
a ton of vaccine that we're going to be able to give to
people. And that sort of makes you wonder, again,

what's our goal here?
So I think we're going to have to specify what groups potentially -- I'm not sure we can do that as that's been described it may be an ACIP issue, but if healthcare workers are first, you know, in line definitely to get vaccine that would make sense. What I'd really like to know and what we didn't get a chance to ask, was the Reagan-Udall group a little bit more about -- they did these analyses of two different populations, the general public, and healthcare workers. It would be really curious to know how healthcare workers felt about getting an EUA vaccine versus one that has been fully addressed in a Phase 3 trial. Because I think they're necessarily going to be people that are more educated and may want to wait until it's been finalized.

And I also have to say that healthcare workers in general, while they are a high-risk group because of exposure, the data does not suggest that they're the ones with the most disease by any stretch because they're the ones with the most PPE. And so I worry about the perception that might come across with that.

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8:05:28
p. 374
DR. MONTO:
Right. So I think that's the problem with healthcare workers. If they have EUA -- if they have PPE the infection rates are very low. But I just put them out a group that's usually listed as being at risk.

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8:05:59
p. 374
DR. NOTARANGELO:
Well, it seems to me that continuation of blinded Phase 3 clinical trials is absolutely critical and so we should do all what we can to make sure they continue. I think, you know, some of the ideas that have been proposed by you and also emphasized by Dr.

Krause are, I think, what we should be doing. So if we issue an EUA -- if we agree on the issue of an EUA, at that point I think the next step would be to have a prioritization of which groups would be entitled to receive the vaccine.

And, you know, healthcare workers may not be the right population but perhaps nursing homes, people running nursing home might be a good population for testing. That would allow, basically, us to gain time so that we would have continuation of blinded Phase clinical 3 trials to accumulate all of the data that are required for full licensure. I wonder whether we can also, you know, invite the FDA to initiate a conversation with ACIP.

I mean, there was, I think it was the Infectious Disease Society representative that proposed a joint action with ACIP and that might be something to consider. But along that line, I think, you know, EUA issuance would not necessarily prevent continuation of blinded Phase 3 clinical, trials and I think that would be important.

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8:07:38
p. 375
DR. CHATTERJEE:
Yes. Thank you. So just a couple of points. One is a follow up which is with regard to who will get this vaccine and how quickly will they get it. As best I understand it, and I'm sure that the sponsors know this in terms of who in their trials, the likelihood that there are a bunch of healthcare workers or first responders who are in their trials I think is fairly small. So, you know, in terms of losing people from the trials because they're the ones who've been prioritized to receive the vaccine earlier on, I think is less likely to happen.
The other thing goes back to a couple of people mentioned this already, which is how quickly do we get this vaccine out to people? You know, it may be actually, even with all the kitting and everything

that's being done to position the vaccine to be pushed out as quickly as it's authorized and licensed, it's probably going to take several months before the vaccine gets into people's arms. And so there will be this lag, there will be this delay during which the data will continue to be accumulated. And so I just wanted to make that point.

The second one is with regard to waning immunity and what happens two months out versus six months out. I wish I could quote you the data, but as probably everyone on this call is aware, the early weeks is going on right now. And I saw a presentation yesterday on seroprevalence studies and, you know, what happens to -- with natural infection, what happens to the immunity. And it seems like, yes there is a waning but then there's a plateau that goes on for several months.

And of course, not having a serologic corridor protection we don't know whether that's sufficient to protect people from infection or from disease. But it certainly doesn't look like it sort of goes up and goes down and disappears.

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8:09:39
p. 377
DR. MONTO:
Waning is something which our group has been studying very carefully with influenza vaccine and you're absolutely right. The waning occurs quickly right after vaccination and then sort of plateaus going out and we really do not understand with coronaviruses what the -- what will be the case, and I think we just have to learn about that as we go forward. One of the questions that we can never ask -- answer about a vaccine when it's licensed is how long it's going to last and whether we're going to need boosters.

https://youtu.be/1XTiL9rUpkg?t=29432
8:10:32

p. 378
DR. COHN:
I want to go back to the
question about the unblinding. And it feels like I
agree with everything Dr. Krause said. But it feels
like there's a difference between actively unblinding
and offering study participants vaccine versus an EUA
being available and somebody potentially being in a
recommended group to get the vaccine, and them making a
choice to go get the vaccine but maybe not knowing -- I
-- what I'm trying to say is that I wonder if all the
study participants understand that they did potentially
get a placebo. And if there's something that you could
do to sort of make study participants aware that if
they are in a recommended group, they could consider
going to get vaccinated while not unblinding the
results, if that makes sense.
I do worry about telling a person that they should not go get vaccinated when they are in one of the prioritized groups, potentially. I also agree that there will be limited doses early and there won't be that many participants in the study who will be recommended for vaccine early.

https://youtu.be/1XTiL9rUpkg?t=29525
8:12:05
p. 379
MR. TOUBMAN: I believe you said that one of the sponsors had sent letters to all the participants saying that --
DR. MONTO: It was to the committee. To our committee. It was sent to our committee.
MR. TOUBMAN: Okay.
DR. MONTO: It's in the file -- the box file that we got.
MR. TOUBMAN: And what did the letter say since I'm not going to look it up right now?
DR. MONTO: The letter says that for ethical reasons they may have to tell the placebo recipients that there is an EUA available vaccine which they can receive.
MR. TOUBMAN: Okay. So here's the thing that occurs to me. It was pointed out by Dr. Krause and others, there may not be enough vaccine anyway, so if it becomes a choice it's not a real choice. But the problem as I understand it is if those people, even though they can't get it now know that they're in the placebo group their behavior may change. That's the whole reason for having a blind study.
DR. MONTO: Exactly. They --
MR. TOUBMAN: Nobody knows if they're protected or not so they all act -- both sides act the same and you basically destroy that if you inform them.
DR. MONTO: I probably shouldn't have brought that letter up. It was in our file and I had some

questions raised by it because of the potential for unblinding which destroys the whole purpose of a randomized trial. But I think we can worry about that when -- if and when that company's product comes before us.
So I apologize for bringing it up. But I just wanted to point out the complexity of this issue and that we should be pretty firm about what we want and what we are unhappy with in terms of continuing the blinding.
MR. TOUBMAN: All right. And obviously, this goes back to the earlier question, but this is a problem. There's no question that we've got a problem here if we do EUA under these circumstances and that's where we should be careful.

https://youtu.be/1XTiL9rUpkg?t=29658
8:14:18
p. 381
MR. TOUBMAN:
And by the way, I did appreciate Dr. -- Cody, talking about why they picked two months. But that's the reason why they chose three months because in the past it's generally been six weeks but with new platforms, we don't know so I'm just -- I'm confused why we're not being willing to be open to extending that period to what the WHO uses. I'll save that for later, I guess.

https://youtu.be/1XTiL9rUpkg?t=29750
8:15:50
p. 382
DR. NELSON:
Dr. Monto, I did want to make a point regarding your concluding summary for question number one for the record. There was a lot of concern about the primary endpoint being in favor, or at least enabling the potential for milder disease, and I hope you captured that as part of the conclusion of the discussion.

With respect to this particular question, number two, I think it is important to make the distinction between continued monitoring of placebo recipients versus ongoing enrollment and the potential for new placebo recipients to receive vaccines.

Two very different scenarios in the presence of an EUA vaccine on the street. And I would highly recommend, since they're asking for recommendations for guidance to industry, that we would ask that those that continue to enroll once an EUA is on the street have a specific plan for when placebo recipients will, at some point, be enabled to receive a vaccine to protect them from this disease.

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8:17:10
p. 383
DR. ANNUNZIATO:
I
wanted to address some of the points and questions that Amanda Cohn and that Dr. Nelson had brought up because we, and I know others, have -- do have experience conducting placebo-controlled trials for approved and available vaccines. And there are a couple of critical considerations that you really need to keep in mind when you're doing studies in this way.
So of course the trial objectives need to address important clinical, scientific questions. And that's the situation that we're talking about here.
And as part of the informed consent process, participants have to receive clear information about the availability of an approved vaccine for them and that they can receive the vaccine outside of the clinical trial that they're being asked to participate in, that they may receive placebo or an unapproved vaccine if they join the study, and how long they're being asked not to be vaccinated with an approved vaccine that they're otherwise, you know, could access.

And when I say the informed consent process, this is something that happens, as you all probably know, not just when a subject or a volunteer first joins the trial. But as the scientific knowledge and the availability of vaccines or treatments evolve during the conduct of the trial, the consent process needs to be, you know, done again so to say, subjects are reconsented to make sure that they're aware of the most current information.

So, you know, we think that these principles would apply if a vaccine were to be granted an EUA or a full approval for COVID and -- but we really need to also think about the feasibility of conducting placebo-controlled studies if in fact there is a vaccine available to the general population, or even to specific segments of the population by an EUA. So this is really going to depend on the specific, I would say indication, but maybe it's really the recommendation, you know, how the EUA approved vaccine would be administered, who would be able to access it, whether or not all the countries that are participating in your trial have approved vaccine provisions as well, and the availability of the vaccine, you know, to the different specific groups who are in your study.

There are a couple other really unique aspects to this situation that have really struck me in listening to people talk today that's going to create additional challenges for investigators and sponsors of these studies. And these might not be actually overcome-able. We'll have to see and think carefully about it. But the great public attention that's being given to this vaccine, to these vaccine development programs, and the strong perception that you know, based on a variety of concerns may in fact preclude continuation of some of these placebo-controlled studies.

We'll just have to monitor and watch this carefully. In fact, if vaccines do become available to the entire U.S. population, I think we heard earlier today that the projections are that, you know, by next summer that may in fact be a reality. And so as I said, you know, this is something we'll have to monitor and watch. But just in general, you know, typically you are able to continue your studies under these circumstances.

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8:21:00

p. 387
DR. MONTO:
Thank you. I just wanted to
remind us all that we have been using observational
data for a lot of effectiveness studies. So what looks
like logistically difficult, maintaining the blind for
very long periods of time may not actually be -- both
not feasible and not necessary as we go forward. And
that's why we're shortly going to get into question
number three which really looks at other kinds of
observations.

https://youtu.be/1XTiL9rUpkg?t=30107
8:21:47
p. 387
DR. KURILLA:
Thank you. Yeah. Just wanted
to make one comment -- follow on a couple of other
comments with regard to the unblinding. And it's my
understanding, Dr. Krause can correct me if I'm wrong,
but I don't think FDA would be issuing an EUA for
specific populations such as healthcare workers or
something like that.

I would assume that they would be issuing an
EUA based on the data for the specific populations
within the trial protocol upon which randomization was
done. And I know, for example, having read one of the
protocols that the randomization was done on
individuals under 65, under 65 with comorbid
conditions; and there was a list of those specific ones
that would put them in that "high-risk category," and
then over 65.

So those would be, I would assume, the
available data sets upon which an EUA would be based.
Now, just because an EUA is issued for people
under 65 doesn't necessarily mean that everybody under
65 gets it. There isn't going to be enough vaccine in
the first place. But that's where a group like ACIP or
other entities are going to have to make a decision on
what risk groups based on exposure, as opposed to just
based on their particular characteristics from the

trial design, would specify. So I don't think that
it's going to really be a major issue in terms of
preventing the ongoing conduct of the Phase 3 trial.

https://youtu.be/1XTiL9rUpkg?t=30210
8:23:30
p. 388
DR. MONTO:
Especially if the vaccine is
available in relatively short supply.

https://youtu.be/1XTiL9rUpkg?t=30232
8:23:52
p. 389
DR. MONTO:
Okay. So we all wish we could
continue unblinded -- or blinded collection of data but
we realize that there may be some problems. We talked
about various scenarios that might be used. And this
is something which we would like to see but if we
cannot, then we move into follow up studies on -- in an
observational setting and therefore we will go into
question number three.
Please discuss studies following licensure and
or issuance of an EUA for COVID-19 vaccines too and
firstly safety, efficacy, and immune markers of
protection. And I -- let's leave out immune markers of
protection because that's a whole different issue. So
let's just look at safety and effectiveness.

https://youtu.be/1XTiL9rUpkg?t=30317
8:25:17
p. 389
DR. ALTMAN-GANS:
I did just want to
put in a plug for in terms of safety, there's a couple
things that I think are problematic. The first one is
that the solicited safety profiles only through day
seven. I think that's problematic and should probably
extend longer than that, but this post-marketing
anyway.
The post-marketing I think from what we heard
earlier is a little problematic in a couple of things.

So the first line people who may be issued this, we heard about healthcare workers, we heard about certain populations. And a lot of them are not going to be included in the databases that are currently being used to monitor these safety events as we go through, particularly the non-passive ones. So (inaudible) is obviously anybody. And so that's really problematic. The problematic issue is also going to be a lag in time. So the number of doses that have to be administered to actually get a signal on BSD or something like that is actually problematic. Again, given the people who are likely to get it first might not be in those systems. So I think we need to be more dynamic and more flexible in how we think about these. I also think we're not utilizing our new platforms. So there was some talk about using the signal system and using BAPP, but it wasn't clear from the presentations that they're actually looking at these. And then using some kind of phone platform where people can also self-report. So I think all those have to be actually incorporated into what we would see in terms of the safety signals moving forward. So I think those are going to be very important.

I would say that in terms of safety we also have to add some other kinds of markers. I'm not going to talk about the markers of protections because I think they're going to do all the B-cell and T-cell studies particular to SARS-COVID-2. I think that's fine and we'll learn something perhaps from that. But the markers that I am particularly interested in are in the pro-inflammatory and pro-thrombotic, which I think need to be part of an ongoing safety signal that would part of that.

https://youtu.be/1XTiL9rUpkg?t=30488
8:28:08
p. 392
DR. CHATTERJEE:
With regard to safety,
I think, you know, particularly studying sub-populations would be important in making sure that this

-- whatever products get licensed or authorized are actually safe in the populations that they might be used in. So that would be one.
The other is the longer-term follow up could be maybe more months to years that might be necessary to identify safety signals that might not show up immediately. And with regard to effectiveness, it's similar kinds of things, particularly as we talked about, you know, the effectiveness against severe disease, and in those populations that are disproportionately affected, as well as how long the immunity actually lasts.

And then with regard to the specific populations, we've talked about this already. For children, I think in terms of immuno-bridging for effectiveness, even though we don't have a serologic corridor of protection but if it appears to be protective in adults perhaps we could look at that. But the safety issue is a very different animal, I think. And I think the studies do need to be done in children to assure that these products will actually be safe for use in children.

https://youtu.be/1XTiL9rUpkg?t=30588
8:29:48
p. 393
DR. NOTARANGELO:
Thank you. So, Dr. Monto, first of all, I would like to endorse your proposal; and not to talk about enhanced respiratory disease but to comment on enhanced disease that would include also all of the vascular thrombotic events that were mentioned before. My other comment is about children. As you heard from my previous comments, at this point I'm not particularly eager to have children as potential candidates for receiving vaccines.
I don't think we have enough data there and I don't think we can use the argument of immuno-bridging because I might see something that's very specific to SARS-COVID-2. We cannot take lessons from other vaccines in that regard. But, in any case, if children at some point are included in the absence of trials or

specifically targeted to children we would need to have safety studies that are long enough in duration to include the potential appearance of MIC and they should be large enough to take those into consideration.

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8:31:06
p. 394
DR. PERGAM:
So one thing we'll definitely be curious when the EUA get presented to us, the possibility is certainly for a lot of these trials, the Phase 1 and Phase 2 data, will have longer-term follow up I would hope. Although I haven't heard that from the companies specifically to determine whether those that were in Phase 2 and Phase 1 trials were followed for prolonged periods to see about waning immunity. Because that could be really interesting information. Even in a small population, it might help us to think about these EUAs. Even with a smaller group and differences in how the vaccine was given, I would be curious to see if that data is going to exist within those patient populations.

And I'm still unsure about the EUA that some of the correlates that they're going to be looking at in these patients. Is there a possibility if an EUA is developed that there can be a requirement for monitoring a new patient similar to what they're doing? I think it was the phone-based app, is the V-Safe app that if they did do an EUA and we had some of these individuals vaccinated, one thing I think we are potentially losing is the ability to follow them closely for potential side effects.

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8:32:33
p. 395
DR. MONTO:
Well, I can't answer for Phase 3 commitments. What I can tell you is that I know that CDC and other agencies are thinking, design your studies to look at long-term effectiveness which will

give you answers about duration of immunity. I think there's also the issue of enhanced disease at -- if there is break-through infection and that could be an infrequent complication which you will need the larger numbers you get in observational studies to pick up. So the observational studies are going to be very important for safety as well.

https://youtu.be/1XTiL9rUpkg?t=30825
8:33:45
p. 396
DR. MEISSNER:
Thank you, Dr. Monto. I would just like to state the fact that I agree with Dr. Notarangelo and apologize if I didn't pronounce that properly but in terms of studies in children. I think it's going to be so important to evaluate any vaccine in children and adolescents before they're included in any sort of a recommendation. I think the rates of disease are nowhere near as high as they are in the high-risk groups, such as individuals over 60 or 65 years of age, they're only a fraction. And we know that MIS-C occurs at a rate, as I think I mentioned earlier, of 2 cases per 100,000. So I would, if I were part of the FDA, I would certainly want to be very convinced of the safety of a vaccine before I recommended or approved its use in children.

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8:35:13
p. 397
DR. GRUBER:
Yeah. I just wanted to clarify for the committee that in regarding studies in children that there is actually a law, the Pediatric Research Equity Act that requires manufacturers of vaccines and other products to conduct studies in children. Of course, we can license a product if we have a -- if the safety and efficacy is established in adults and we would not have to hold up licensure.
But the vaccine manufacturers really have a, you know, and that's mandatory. They need to submit a pediatric study plan. And they are -- they need to

outline the studies that they plan to conduct in children. And so we will be getting data on safety in the subject population. I just wanted to clarify that.

https://youtu.be/1XTiL9rUpkg?t=30972
8:36:12
p. 398
DR. MEISSNER:
Thank you, Dr. Gruber. I, as a pediatrician, completely concur on the importance of including children in the clinical trials. But I think they need to be evaluated as a distinct group with phased evaluations just as is being done in adults because the pattern of disease is quite different in children and I -- lumping them in with adults in this -- with this particular illness I -- would cause me some discomfort.

https://youtu.be/1XTiL9rUpkg?t=31023
8:37:03
p. 398
DR. KRAUSE:
Thank you. Yeah. The few comments regarding safety, I think we need to recognize that there's a lot of new platforms here that are being utilized. And so rather than our traditional, let's do vaccine by vaccine, I think there needs to be a concerted effort to see whether or not there's some long term effects or impacts overall on the health of people with regard to specific platforms or -- and or novel adjuvants that may be included. We need to try to -- we need to have a systematic way of not just that's one aspect.

You know, with regard to children in particular but I think in general, you know, it's been mentioned before, we don't have a correlative protection. And I think it's also rather interesting and rather paradoxical finding that individuals with low -- with mild or even asymptomatic infections tend to have low serologic titers in response to the infection. The degree of antibody titers seems to be positively correlated with the severity of infection,

which suggests either that the asymptomatics are having a very rapid antibody response that goes away quickly, or they actually have an antibody independent response that is mediating the host defense.

That may be going on in children more so than in adults and I wonder if that we're -- it's not that introducing neutralizing IGG cannot work as a vaccination strategy, but I wonder the potential that we may be circumventing a more natural response to the infection may have some downstream impacts. So I think we need to be a little cautious about that until we really start to understand the correlates of protection from natural infection so we can relate how that impacts what the vaccines are doing.

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8:39:08
p. 400
DR. MONTO:
Thank you. And the reason I said I didn't want to talk about immune markers of protection is that I think that is a very complicated issue and it's not only going to be -- we're not going to learn only from breakthrough infections and things like that in the vaccinated but also from natural infection.
As we -- since we're getting pretty late and we have point B, I want those who have their hands raised to try to bring in also the issue of specific populations. I'm not sure that we haven't gone over this already so it may not be necessary to handle it separately, but I do think that we want to cover that as well. And we do have -- we're coming up to -- we're getting close to our stop -- we're beyond our closing time already and I really would like to stop before 7:00.

https://youtu.be/1XTiL9rUpkg?t=31235
8:40:35
p. 401
DR. NELSON:
I do think it's critically

important that we do extend the study of those populations that are currently encouraged to be in the current clinical trial. In particular, the people of color and those disproportionally affected by infection itself. But also to take heed from some of the advice we heard from public testimony and from our own experience of noting that there are gender differences in immune response as well as safety and efficacy from vaccines. Those two particular ones.
But I think it's also important for us to remember who's not being involved in the current clinical trials. And all you have to do is look at the exclusion criteria of several of these trials. Those with allergic diseases that might be or likely exacerbated by vaccination, the immunosuppressed we did hear about earlier, history of primary malignancy or ongoing malignancy, bleeding disorders, uni- -- or really multi-organ disease that is severe.
There are a lot of individuals out there who will be waiting for the licensure piece to have access to this vaccine, and specific study of immune responses of those critical populations I think is needed as well as safety.

And if you look at some of those disease states it's also disproportionately affected by people of color and opportunities for us to generate real data and improve the trust in the vaccination process if we specifically study efficacy in those individuals.

One thing I haven't heard today is that we do need to generate specific data on vaccine co-administration. So it is critically important that we understand the interplay of this vaccination in the context of our routine schedule. And frankly, right now in the midst of catch up for all those who've deferred their routine vaccinations as a part of pandemic mitigations the last several months.

Another point I'd like to bring up, moving back to A is, I agree with Dr. Kurilla. They're new platforms, there are new opportunities for rare adverse events. As an allergist, I was particularly intrigued

to understand that two of the vaccines are relying on T-2 hypersensitivity immune responses. It may take several months for some of these exacerbations to come to fruition and show themselves through passive reporting systems.

And the fourth point, I think we need to be very explicit in that there needs to be some intentional study of duration of immunity as part of these post-marketing surveillance studies.

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8:43:15
p. 403
DR. MONTO:
Thank you, Dr. Nelson. I think we -- what I would like to do first is to attempt to summarize what we've heard about the post-marketing, post-licensure studies. That these are absolutely necessary for duration of immunity or safety, particularly because we are using new platforms. That we should look at this not only by-product but also by platform because there may be commonalities to any untoward effects that are seen based on the platform, as well as the product.

We absolutely need to have population specific data in terms of minority groups, women, men, and the rest. And the beauty of observational studies as vaccines are rolled out is that your numbers increase and you don't have -- if a vaccine uptake is there you don't have the numbers problems that you do, and the volunteerism problems that you have in the clinical trials. So we are all in favor of these kinds of studies, correlates of protection are going to be critical. Also correlates of natural disease. This is something which is novel to our populations, at least SARS-COVID-2 is. Seasonal coronaviruses have been around for a while. We know a lot about them, but they -- we do not see the kind of pathogenesis that you do with this infection. So everything is on the table in terms of studies.

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8:46:37
p. 405
DR. GRUBER:
Thank you for giving me two minutes. I just wanted, before you adjourn the meeting and I know it is very late hours, but, you know, I want to also thank the committee for their very thorough discussion here. We know this is a very difficult and complex issue but if I can summarize real quick for what I've heard and, Arnold, you shake your head or you nod. Okay?
But in terms of the guidance documents and the approaches for safety and effectiveness data as we outlined them, I heard that the general principals and the standards that we are applying are right on the money and that there is really buy-in for that. I hear there is some concerns and suggestions made for some of the details the importance for making sure minorities are included in clinical studies. We had some discussion from endpoints.
We can take this forward if we have, you know, new vaccines entering clinical studies. It may be a little bit difficult for those who are already in Phase 3. We hear you on the bridging issue with the peds population.

What I want to know from you, the two months -- the median two months follow up that we said and the EUA as for people expressing some concern with that being maybe not short enough. But, you know, if it then cannot be longer by no means should it be shorter than two months of median follow-up. That's what I heard.

And in terms of the blind, I think that was keeping the blinded and the placebo comparator on even though you have an EUA. You said even though we all would like for this to continue but we have to realize that at some point we can't really maintain the blind. But do I hear you saying, and do I hear the committee saying that the blind should be maintained for as long as feasible and there should not necessarily be an

automatic cross-over of the placebo recipients to active -- to getting the vaccine?

https://youtu.be/1XTiL9rUpkg?t=31736
8:48:56
p. 407
DR. MONTO:
I think that that is very clearly what you heard. I don't think there's been any doubt about that point. I think there may be some questions about the two months and also some of the outcomes that are being used. And as somebody who's worked flu vaccines for a long time, what you are using as the outcome is standard for most respiratory vaccines. And we learned about some of the other outcomes either as secondary outcomes in the randomized trials or in observational studies. So I fully agree with your summary.