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COVID-19 Vaccine Development: Where do we go from here?

Jonathan Hartzel, Merck & Co., Inc., North Wales, PA, USA

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https://www.nytimes.com/2020/12/11/health/pfizer-vaccine-authorized.html

F.D.A. Clears Pfizer Vaccine, and Millions of Doses Will Be Shipped Right Away

An initial shipment of about 2.9 million doses of the vaccine will be sent around the United States over the next week.

By Katie Thomas, Sharon LaFraniere, Noah Weiland, Abby Goodnough and Maggie Haberman

Published Dec. 11, 2020 Updated Jan. 8, 2021

https://www.cnbc.com/2020/12/18/moderna-covid-vaccine-approved-fda-for-emergency-use.html

HEALTH AND SCIENCE

FDA approves second Covid vaccine for emergency use as it clears Moderna's for U.S. distribution

PUBLISHED FRI, DEC 18 2020•7:38 PM EST | UPDATED FRI, DEC 18 2020•7:59 PM EST

Berkeley Lovelace Jr.
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SHARE

Johnson & Johnson hopes to submit emergency use authorization application next month for its vaccine

By **News 12 Staff** | Jan 05, 2021, 12:41pm EST | Updated on: Jan 05, 2021, 12:41pm EST

https://bronx.news12.com/johnson-and-johnson-hopes-to-submit-emergency-use-authorization-application-next-month-for-its-vaccine

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Where do we go from here?

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- Despite two highly efficacious vaccines, the development of additional COVID-19 vaccines needs to continue:
  - One-dose vaccine
  - Durability of protection?
  - Safety profile
  - Storage characteristics (-70˚C, -20˚C, refrigerator stable?)
  - Supply challenges

- How should future efficacy trials be designed?

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Pfizer/Moderna VRBPAC Discussions

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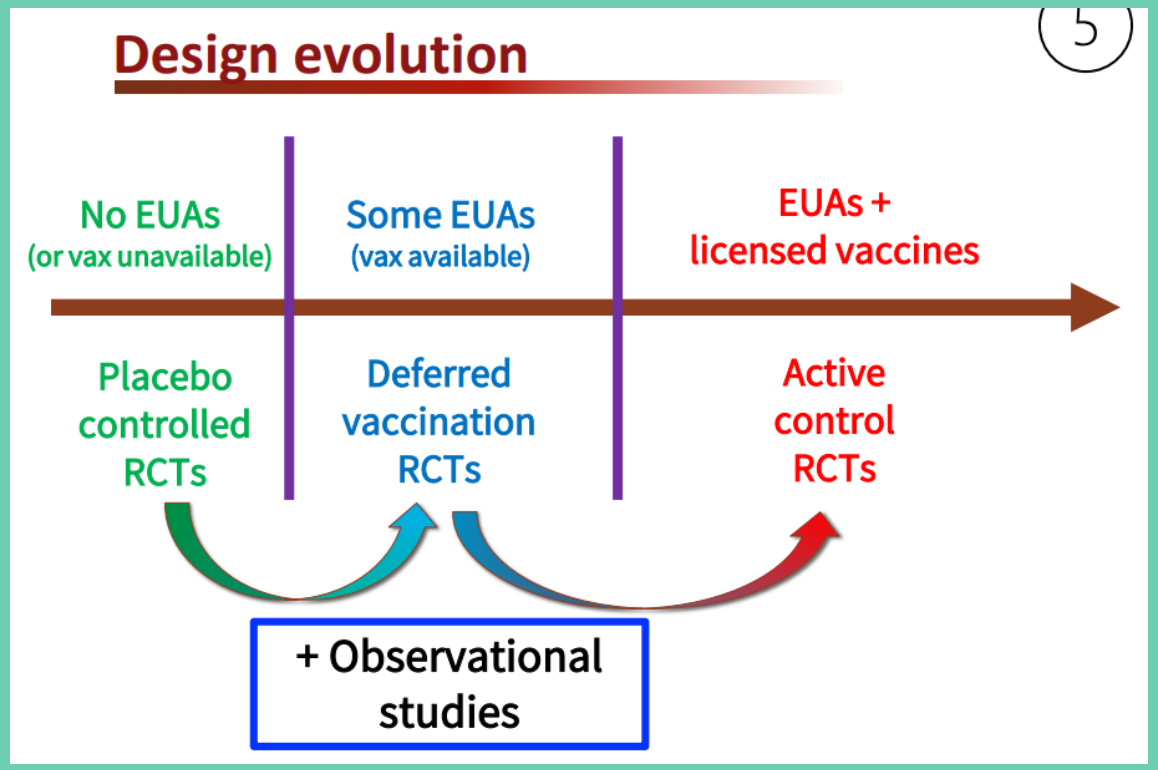
- Steven Goodman† "Considerations for placebo-controlled trial design if an unlicensed vaccine becomes available"



†Assoc. Dean, Clinical and Translational Research Professor of Epidemiology & Population Health and Medicine, Stanford U.

https://www.fda.gov/media/144354/download https://www.fda.gov/media/144582/download

Pfizer/Moderna VRBPAC Discussions

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HEALTH

Pfizer and BioNTech speed up timeline for offering Covid-19 vaccine to placebo volunteers

By MATTHEW HERPER @matthewherper / JANUARY 1, 2021 Reprints

https://www.statnews.com/2021/01/01/pfizer-and-biontech-speed-up-timeline-for-offering-covid-19-to-placebo-volunteers/

+ Observational studies

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Blinded, Placebo-Controlled Trials

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- "Gold-standard" design – provides the most reliable and unbiased information
- Operationally challenging once vaccines become available.
- What about ethics? "No Bright Lines" (Goodman)

Ethical implications of COVID risks

- Maximum 6 mo. vaccine benefit ≈ 1/200 reduction in serious disease and ≈ 1/1000 reduction in death.
- This degree of benefit is far lower than the effect of most therapeutics for which we routinely allow placebo-controlled trials, as can be seen in meta-analyses.
- Also, w/o a vaccine many people can lower their risk of infection and thereby lower their COVID risks.

- Therefore placebo-controlled vaccine trials are ethically permissible as long as there are still important things to learn, whose importance are amplified by the pandemic. Such trials may be *infeasible*, but they are not "unethical".

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Delayed Vaccination Trials

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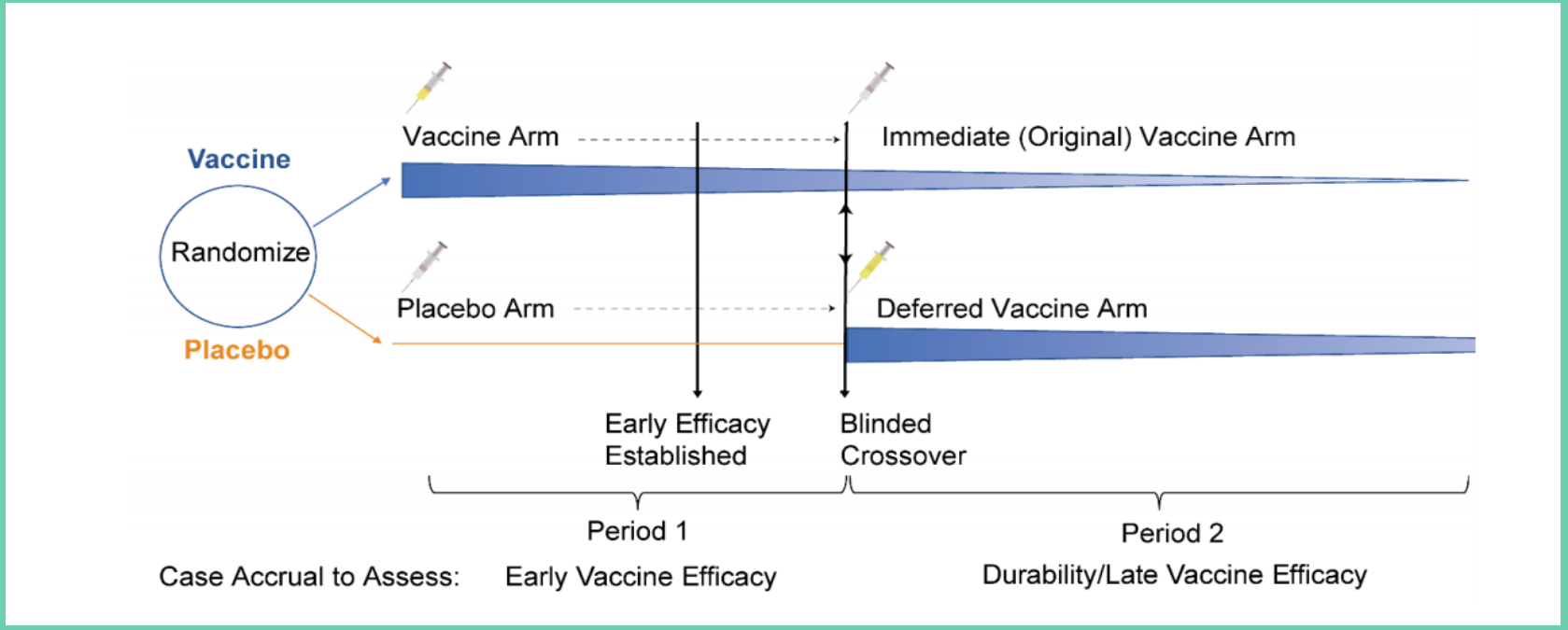
- Blinded, randomized, placebo-controlled study with crossover between vaccine and placebo arm†



† Follmann et al., "Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials", www.medrxiv.org/content/10.1101/2020.12.14.20248137v1

Delayed Vaccination Trials (cont)

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- The Period following crossover can provide assessments of:
  - Durability
  - Waning efficacy
  - Enhanced disease
  - Long-term safety

- Longer pre-crossover period (greater case-counts) will provide better estimates of efficacy in the post-crossover period.

Follmann et al.,"Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials", www.medrxiv.org/content/10.1101/2020.12.14.20248137v1

Delayed Vaccination Trials (cont)

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- Important to treat participants in both groups the same by "vaccinating" each at the crossover in a blinded manner.
  - Participant behavior could change if they know they are getting the vaccine.
  - Assessment of symptoms could be biased if vaccination status is known.

Follmann et al.,"Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials", www.medrxiv.org/content/10.1101/2020.12.14.20248137v1

Delayed Vaccination Trials (cont)

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- A compromise from the “gold standard” that still allows for assessment of durability, safety, and CoP after the blinded crossover.
- Still carries ethical considerations and operational challenges as vaccines become publicly available.

Follmann et al.,”Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials”, www.medrxiv.org/content/10.1101/2020.12.14.20248137v1

Active Controlled Efficay Trials (Non-inferiority)

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- The June 2020 FDA COVID-19 guidance states:

  - If the availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with non-inferiority hypothesis testing.

  - For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.

Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance, https://www.fda.gov/media/139638/download

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Non-inferiority margin

Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance, https://www.fda.gov/media/139638/download

Active Controlled Efficacy Trials (Non-inferiority)

- Statistical criteria for placebo-controlled efficacy trials:

  H_0: $VE_P \leq 30\%$,
  VE point estimate of at least 50%.

- Statistical criterion for active-controlled efficacy trials:

  H_0: $VE_{AC} \leq \delta = -10\%$,
  where δ is the non-inferiority margin.

- $VE_{AC}=0\%$ implies that VE_P for the test vaccine is the same as the VE_P for the control vaccine.

- What about $\delta<0\%$?

Test VE Relative to Placebo

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Test VE Relative to Control Vaccine	Control VE Relative to Placebo				
	55%	60%	70%	80%	90%
20%	64.0%	68.0%	76.0%	84.0%	92.0%
15%	61.8%	66.0%	74.5%	83.0%	91.5%
10%	59.5%	64.0%	73.0%	82.0%	91.0%
5%	57.3%	62.0%	71.5%	81.0%	90.5%
0%	55.0%	60.0%	70.0%	80.0%	90.0%
-10%	50.5%	56.0%	67.0%	78.0%	89.0%
-25%	43.8%	50.0%	62.5%	75.0%	87.5%
-50%	32.5%	40.0%	55.0%	70.0%	85.0%
-75%	21.3%	30.0%	47.5%	65.0%	82.5%

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Total Cases Needed for 90% Power

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NI Margin Relative to Control Vaccine	Assumed Control VE Relative to Active Vaccine				
	0%	5%	10%	15%	20%
-10%	4700	2000	1100	650	430
-25%	870	580	400	300	220
-50%	280	220	180	140	120
-75%	150	120	110	90	70

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Active Controlled Efficacy Trials (Non-inferiority)

- Sample Size considerations:
  - Pfizer incidence in the Vaccine arm: 3.6 cases/1000 pyrs
  - 150 cases would require ~42,000 person-years, assuming 0% VE_{AC}
    - 42,000 participants followed for one year
    - 63,000 participants followed for 8 months
    - 84,000 participants followed for 6 months

Active Controlled Efficacy Trials (Non-inferiority)

- Challenges for NI
  - Assumption for the VE_{AC}
  - Assumption for the Active Control incidence (possible declining attack rate?)
  - Justification for NI margin
    - Depends on VE_{AC}
    - Single-dose versus two-dose vaccines

Active Controlled Immunogenicity Trials

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- If a correlate of protection (CoP) can be identified, non-inferiority immunogenicity trials could be considered.
  - Size of trials are much more manageable.
- Identifying a CoP could be challenging given the high efficacy of the current vaccines.
- Joint effort in combining data from the various studies will be needed.
- Can a CoP derived from one vaccine platform be applicable for another platform?

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Future of COVID-19 Trials

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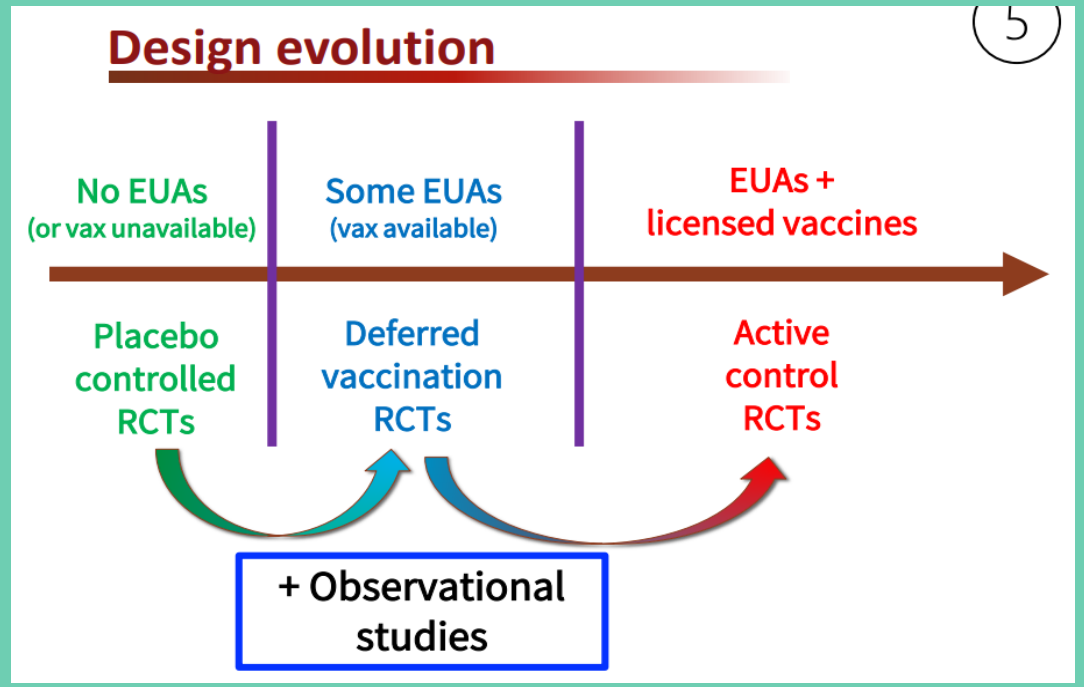
- While broad categories can be defined, many SPONSORS will have development programs that span the categories.
- Continued development will be challenging and require flexibility in both program design as well as regulatory review.



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THANK YOU

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