Covid-19 Vaccine Trials

Peter Doshi, PhD

Associate professor, University of Maryland School of Pharmacy

Associate editor, The BMJ

https://faculty.rx.umaryland.edu/pdoshi/

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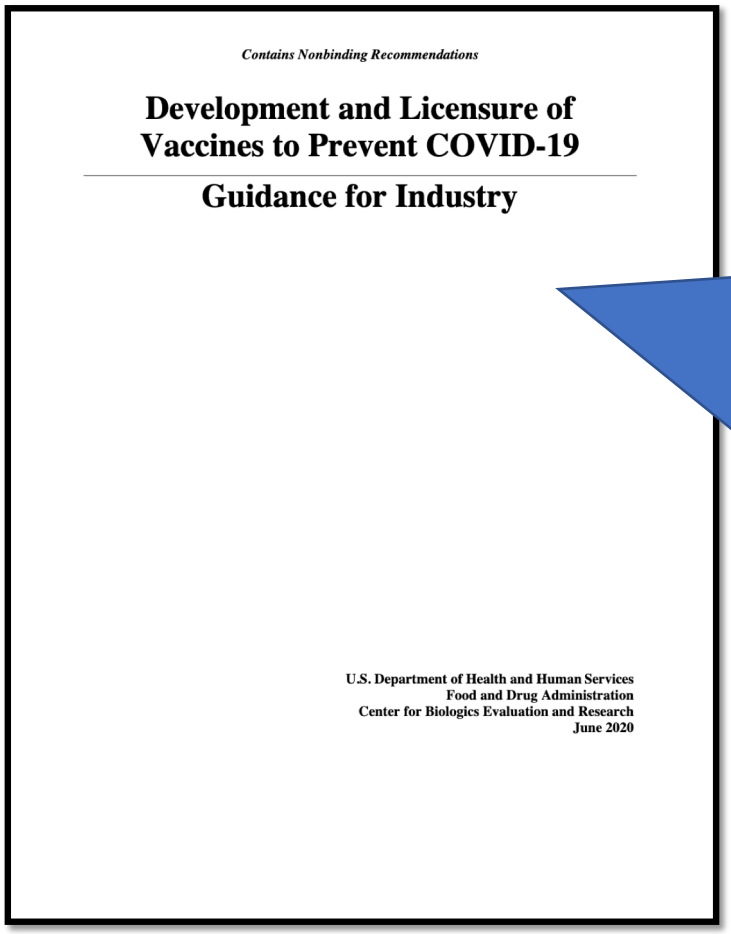
FINANCIAL DISCLOSURES

I have received travel funds from the **European Respiratory Society (2012)** and **Uppsala Monitoring Center (2018)**; grants from the **Laura and John Arnold Foundation (2017-21), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18),** and **UK National Institute for Health Research (2011-14);** and am a paid editor at **The BMJ** and unpaid member of the **Reagan-Udall Foundation for the FDA**.

Summary

- Salary from University of Maryland & The BMJ
- Public, foundation, and non-profit funding of academic research
- Reimbursement (e.g. lodging, travel) from non-profits
- No industry funding

Primary endpoint in phase 3 trials needs revising



Contains Nonbinding Recommendations

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2020

Presence of **at least 1** of the following symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

+ Lab-positive test

Even a mildly symptomatic person could meet these criteria.

Source
FDA Guidance. June 2020, Page 13. https://www.fda.gov/media/139638/download

Study endpoints

- **Phase 3 Covid-19 vaccine trials are designed to test:**
  - Whether they reduce symptomatic Covid-19 (of **any severity**)[1]

- **The trials are not designed to provide definitive evidence regarding:**
  - Whether they reduce the risk of **severe Covid-19, hospitalization, ICU use, or death**[1]
  - Whether they **reduce spread** of the disease[2]
  - Efficacy in **important subgroups at highest risk** (elderly, frail)

Sources
1 Doshi P, Topol E. "These Coronavirus Trials Don't Answer the One Question We Need to Know" https://nyti.ms/2GW51t8
2 Finn A, Malley R. "A Vaccine That Stops Covid-19 Won't Be Enough" https://nyti.ms/2Fwr098

Most Americans Expect Phase 3 studies to be testing whether the vaccines save lives

NIH Press Release, July 27: "As secondary goals, **the trial also aims to study whether the vaccine can prevent severe COVID-19** or laboratory-confirmed SARS-CoV-2 infection with or without disease symptoms. **The trial also seeks to answer if the vaccine can prevent death** caused by COVID-19 and whether just one dose can prevent symptomatic COVID-19, among other objectives."[1]

Sources
1 NIH. "Phase 3 clinical trial of investigational vaccine for COVID-19 begins" https://bit.ly/3duUvoh

FDA's "severe Covid-19" endpoint needs revising

Currently, a mild Covid-19 case with SpO2 ≤ 93% would qualify

FDA's definition needs revising because SpO2 ≤92% in 1 in 20 normal, asymptomatic, community dwelling ≥65+ population

Table 2. Peripheral Blood Oxygen Saturation According to Age and Sex

Method	%, Median (Interquartile Range)	Percentile 5,%	Percentile 1,%	N
≥65				
Total				
Method 1	96.0 (94.0–97.0)	91.0	85.0	636
Method 2	96.0 (94.0–97.0)	**91.8**	80.0	182
Female				
Method 1	96.0 (95.0 -97.0)	91.0	86.4	418
Method 2	96.0 (94.0–97.0)	**91.0**	87.6	106
Male				
Method 1	95.0 (94.0–97.0)	88.0	84.4	218
Method 2	95.0 (94.0–97.0)	**92.0**	80.0	76
≥80				
Total				
Method 1	96.0 (94.0–97.0)	89.0	83.9	399
Method 2	95.0 (94.0–97.0)	**90.7**	84.4	77
Female				
Method 1	96.0 (94.0–97.0)	89.0	81.6	264
Method 2	96.0 (94.0–97.0)	**90.2**	87.0	52
Male				
Method 1	95.0 (94.0–97.0)	89.0	85.2	135
Method 2	95.0 (94.0–97.0)	**89.1**	84.0	25

Method 1: excluding cases with factors influencing the results, according to the multivariate analysis (dyspnea at the moment of examination and history of chronic obstructive pulmonary disease).

Method 2: (author's recommended limit in bold face): more-restrictive analysis excluding cases with factors influencing the results, according to the bivariate analysis. Dyspnea and history of asthma, chronic obstructive pulmonary disease, use of specific respiratory medications, cardiac disease, anemia, or smoking were excluded.

Source: Rodríguez-Molinero et al. 2013 J Am Geriatr Soc, 61: 2238-2240. https://doi.org/10.1111/jgs.12580

What approval should stand for

- **Phase 3 trials should provide a definite assessment of efficacy against the outcomes most important to Americans and public health: severe Covid-19, hospitalization, ICU use, and death**
- **Proof of efficacy is most important in subgroups at highest risk (elderly, frail)**
- **Licensing a vaccine without knowing these things carries major risks**
- **The trials are ongoing and FDA's criteria for judging efficacy can and should be made more stringent**

Contact: Peter Doshi, PhD, https://faculty.rx.umaryland.edu/pdoshi/