

## Beware of covid-19 vaccine trials designed to succeed from the start

**Opinion by William Haseltine**

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In response to widespread demand for more transparency, pharmaceutical companies Moderna and Pfizer have released clinical study protocols for their covid-19 vaccine trials. The goal is to reassure the public that the trials are being conducted responsibly and that any approved vaccine would be safe for all.

But the protocols should heighten anxiety rather than alleviate it. A close reading suggests the clinical trials have been designed to ensure the greatest possible success for these candidates — and that could overstate their effectiveness.

In both the Moderna and Pfizer trials, for example, the primary objective is to prevent any occurrence of covid-19, not necessarily a severe case. Preventing serious illness is a secondary objective. Yet it is the severe cases of covid-19 that have killed nearly 1 million people worldwide and left many millions more with long-term damage. With the current protocols, it is conceivable that a vaccine might be considered effective — and eventually approved — based primarily on its ability to prevent mild cases alone.

If we were developing a vaccine for a simple cold virus, perhaps this would indeed be enough. But covid-19 is far from a common cold. People are not concerned about the tickle in their throat or a runny nose; they are concerned about being put in the hospital. A covid-19 vaccine should, first and foremost, protect us from severe instances of the disease.

Equally troubling is the size of the group in which efficacy for each vaccine would be proved. Both Pfizer and Moderna have touted the large number of participants in their trials, at upwards of 30,000 participants slated for each. But while the full trial sizes might be large, the protocols suggest that efficacy can be proved in an initial test group of just 106 for the Moderna vaccine and in a group of 64 for Pfizer. But keep in mind only half of each group receives the vaccine; the other half receives a placebo.

The protocols suggest that successful initial interim trials for the Moderna and Pfizer vaccines would show efficacy among 74 percent and 76.9 percent of participants, respectively. This means if 39 of those who receive the vaccine do not get sick, Moderna will consider the vaccine a success. For Pfizer, the number is 25.

At this point, the Food and Drug Administration could grant emergency-use authorization. In other words, the two vaccines could hinge on the combined results of 64 people.

Granted, proof of efficacy in such a small group doesn't guarantee that a vaccine candidate will be approved for manufacturing and use worldwide. But the U.S. government has shown that it's willing to rush new anti-covid-19 drugs to market on promises of even less. Were these two vaccine-makers to come out with early results from an interim analysis of their trials and claim their candidates to be effective, there is little doubt the FDA would grant an emergency-use authorization. The public would likely take such a decision as a sign that the vaccine is completely effective, despite the fact that it would have been proved effective only in a small sampling of individuals and might not be useful at all in preventing severe cases of the disease.

While both companies say they would continue their trials and continue to explore potential long-term health risks, it might not be possible to do so if participants receiving the placebo demand the real vaccine. As we saw with previous emergency authorizations — namely hydroxychloroquine, convalescent plasma and remdesivir — once they were granted, the trials ended. Are we really willing to conclude a drug is safe based on the health outcomes of so few?

Recent trials by AstraZeneca were paused after a patient developed symptoms of an inflammatory spinal disease. Rushed Moderna and Pfizer trials could bring about similar short-term health consequences or, potentially far worse, lead to long-term health consequences that we won't discover until months or years after the vaccine's approval.

At a time when an average of 40,000 cases and nearly a thousand deaths are reported every day in the United States — and far more globally — these protocols are outrageous. The fact that one would base the health of billions of humans on the outcomes of a few defies any definition of common sense.

If — or perhaps when — positive early results from these trials are announced, keep my warnings in mind. These protocols seem designed to get a drug on the market sooner rather than later, on a timeline arguably based more on politics than public health. The lives of millions are at risk; we can and should demand better.