Ballad Health COVID-19 Vaccine Workgroup Newsletter

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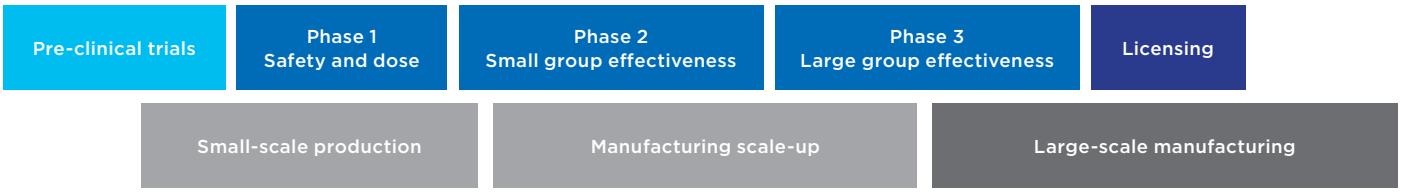
In this issue: How are new vaccines known to be safe and effective?

Vaccine development is a complex process, which is based on over 80 years of experience. From the late 1940s through 2010, vaccine development successfully produced safe and effective vaccines for serious illnesses such as smallpox, diphtheria, pertussis, tetanus, polio, measles, mumps, rubella, hepatitis B, varicella, hepatitis A, influenza, rotavirus, and multiple strains of pneumococcal pneumonia. Vaccine development relies on randomized, controlled clinical trials of sufficient statistical power. Our focus will be on the three clinical phases of vaccine development.

Phase I tests safety, dosage, and immunogenicity in a small number of healthy volunteers. For example, the Moderna mRNA-1273 vaccine Phase I trial involved 45 volunteers who received various doses of the vaccine. (https://www.nejm.org/doi/full/10.1056/nejmoa2022483)

Phase II is randomized, placebo controlled, and involves several hundred volunteers including people at risk of acquiring the disease. The goals are to better understand the vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery. (https://clinicaltrials.gov/ct2/show/NCT04405076?term=NCT04405076&draw=2&rank=1)

Usual vaccine development process



COVID-19 vaccine development process

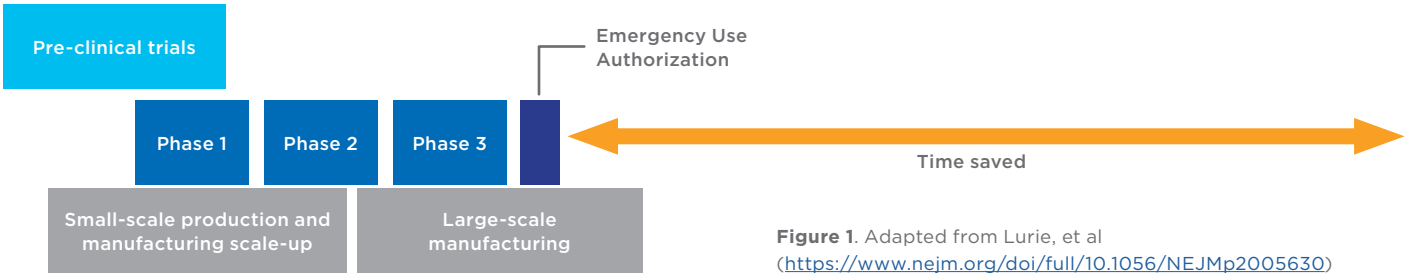
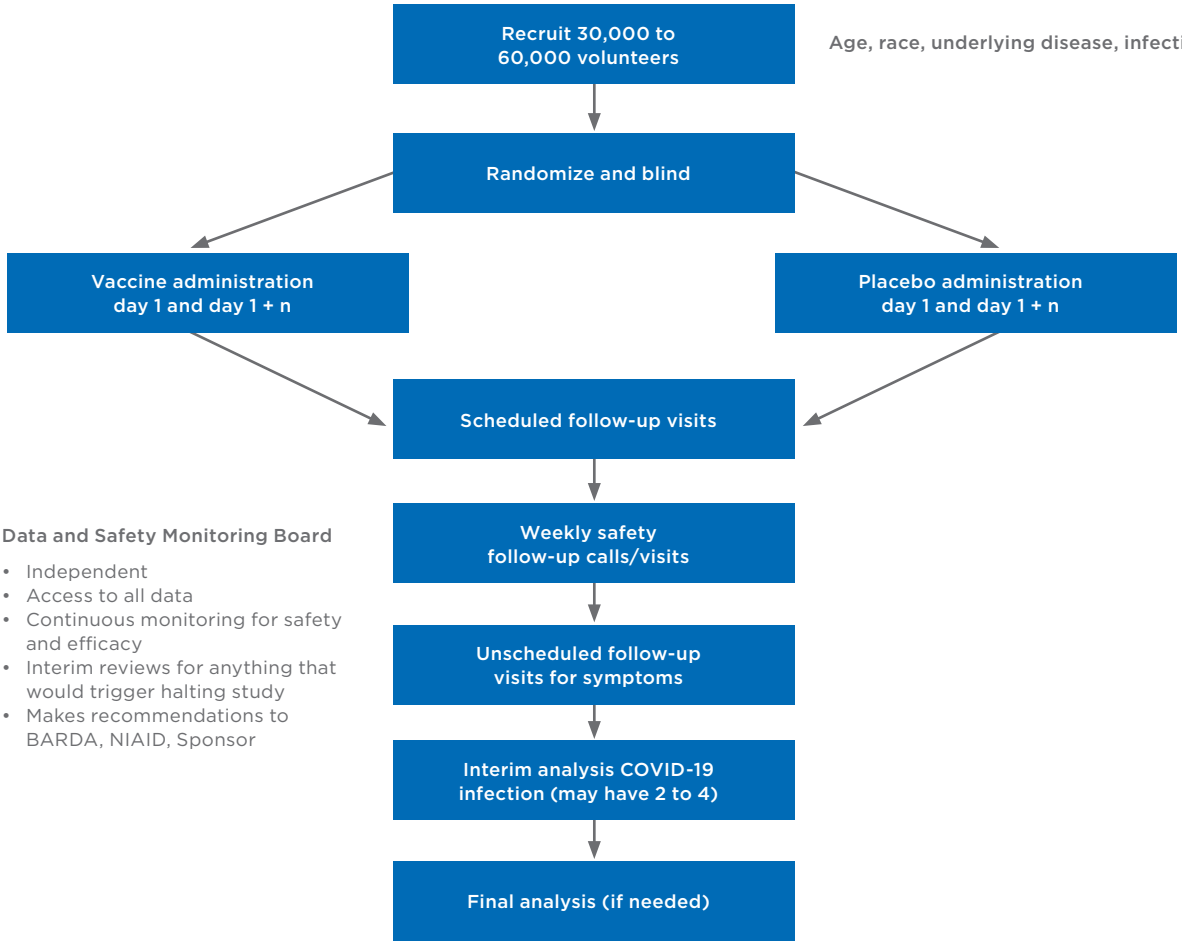


Figure 1. Adapted from Lurie, et al (https://www.nejm.org/doi/full/10.1056/NEJMp2005630)

Phase III is a much larger trial to assess safety and efficacy in tens of thousands of people from groups which are at risk of the infection. FDA said it expects COVID-19 trials to enroll 30,000 to 60,000 people reflective of the groups of people who are at highest risk of morbidity and mortality from COVID-19. It is expected to show if the vaccine can protect at least 50% of people who receive it from infection and to identify any relatively rare side effects which may have not been identified earlier. The overall process for a Phase III trial is shown in Figure 2.

Phase III Vaccine Study Overview

Figure 2



Data and Safety Monitoring Board

- Independent
- Access to all data
- Continuous monitoring for safety and efficacy
- Interim reviews for anything that would trigger halting study
- Makes recommendations to BARDA, NIAID, Sponsor

Primary Endpoint: COVID-19 infection

Table 13: Interim Boundaries Using O'Brien-Fleming Spending function, Calculation Based on the PP Set for the Primary Efficacy Endpoint

Information Fraction (% of total #cases)	Number of Cases	Nominal Alpha	Efficacy Boundary Rejecting H0: VE ≤ 30%	Cum Prob (crossing efficacy boundary if the true VE = 60%)
IA1 35%	53	0.0002	VE ≥ 0.741 (HR ≤ 0.259)	4.6%
IA2 70%	106	0.0073	VE ≥ 0.565 (HR ≤ 0.435)	61.5%
Primary analysis 100%	151	0.0227	VE ≥ 0.495 (HR ≤ 0.505)	90.0%

Abbreviations: HR = hazard ratio; IA: interim analysis; LB = lower boundary; PP = per-protocol; VE = vaccine efficacy.

The clinical trial is large enough that it can detect 60% vaccine efficacy with a 95% confidence interval.

https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf

How do we know if a new vaccine is safe?

Using a randomized, placebo-controlled trial design is the best way to assess safety of the vaccine. Adverse effects may occur in either arm of the study, and thousands of participants are necessary to identify relatively rare adverse events.

Adverse events are actively monitored and, if severe, lead to pausing new enrollment so a thorough review can be done to assess the possible link with the vaccine. For example, AstraZenica paused its phase III trial due to a serious adverse event (transverse myelitis) in one volunteer on 9/6/2020 to investigate. It resumed the trial in the US on 10/23/2020.

During the study, the independent Data and Safety Monitoring Board has access to blinded and unblinded data, including who received the vaccine and who did not (see https://www.fda.gov/media/75398/download). The Board monitors the results of the vaccine trial as it is happening, both for adverse events and for measures of efficacy or lack of efficacy. The Board makes recommendations when action is indicated to the vaccine sponsor and to outside agencies, such as the FDA and the Biomedical Advance Research and Development Authority (BARDA), which is under Health and Human Services.

Vaccine side effects are proactively sought and measured in pre-determined categories and degrees of severity. Trials use a combination of routine visits, calls, and review of self-report logs weekly. After each vaccine dose, volunteers are followed daily (usually for 14 days). If side effects or clinical illness occur, the frequency of monitoring increases. If serious adverse events occur, clinicians will evaluate the volunteer and assure timely medical care. Serious adverse events are reported to the Data and Safety Monitoring Board.

Even after the vaccine trial is complete, which may take two years, several mechanisms will be used to detect possible safety issues with any new vaccines. The most prominent means is the Vaccine Adverse Event Reporting System (VAERS) which was established in 1990. It is run by CDC and the Food and Drug Administration (FDA). Details are available here: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html

How do we know if a new vaccine is effective?

Primary and secondary endpoints are used to measure vaccine effectiveness. The primary endpoint is COVID-19 infection in the vaccine group compared to the placebo group. The number of volunteers in the vaccine trial is based on the expected number of infections during the trial period. The statistical analysis of possible outcomes which would demonstrate efficacy or non-efficacy have been performed and shared (see Figure 2).

Secondary endpoints may include vaccine efficacy to prevent severe COVID-19, serologically confirmed COVID-19, and/or symptomatic COVID-19. Secondary analysis for production of protective immunity may include: Production of protective antibodies (humoral immunity), production of other longer-lasting cell-mediated immunity, and comparison of the strength of immunity with that produced by COVID-19 infection.

Once a vaccine trial has produced evidence of safety (with at least 50% of volunteers having been followed for at least 8 weeks after the last vaccine dose), and efficacy (with at least 50% vaccine effectiveness), then the vaccine sponsor can submit an application to the FDA for Emergency Use Authorization.

For additional detail, please see COVID-19 vaccine trackers:

Vizient is a healthcare performance improvement company Vizient vaccine tracker

The Regulatory Affairs Professionals Society (RAPS) https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

The New York Times tracker has won wide endorsement, including from the Hopkins Coronavirus Resource Center COVID-19 Vaccine Tracker

Members of the COVID-19 Vaccine Workgroup

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