

The Road to Safe and Effective Vaccines

Clinical trials and their role in providing lifesaving vaccines

WHAT IS A CLINICAL TRIAL?

Each year across the world, manufacturers complete research and testing in the hope of creating a new vaccine, one of the most cost-effective public health interventions. The vaccine development process occurs in stages, as the vaccine is carefully evaluated in the laboratory, in animals, and finally, in humans. The rigor of the process ensures that safe and efficacious vaccines reach the public. Two major types of studies are conducted during vaccine development: testing in a laboratory and animals (preclinical studies) and testing in people (clinical studies). The vaccine is thoroughly tested in the laboratory and in animals before it is given to people—a crucial step in moving toward a licensed vaccine.

Clinical studies, or clinical trials, are research studies in people that answer questions about a product's safety, immunogenicity, and protective efficacy and that follow a pre-defined set of rules and regulations. Clinical trials have four main parts, or phases; each phase builds on the information received from the previous one, and with each phase the number of participants increases. Clinical trials have historically been an important step in evaluating new drugs and vaccines; however, with the creation of regulatory authorities, such as the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products, clinical trials are now required to approve new vaccines.

HOW DOES A CLINICAL TRIAL WORK?

Ensuring that the trial is properly designed is the first step in the process. Clinical trials vary in size and location; however, they all work based on certain guidelines that help to ensure the safety of participants and the rigor of the information that is gathered. A key element in determining the design of a clinical trial is the intended use of the vaccine. The intended recipients of the vaccine determine where clinical trials will be conducted and in what groups of people. For example, a vaccine intended for global use will most likely be tested in both developed and



PATH / Robin Bletlik

developing countries, while a vaccine to address diseases that occur in some countries and not others (e.g., tropical diseases) will require a clinical trial in specifically-affected countries. Similarly, a vaccine designed to fight a disease in elderly populations will be tested in the elderly after initial tests are completed in healthy younger adults.

In order to effectively study a vaccine, it must be compared to an alternative. In clinical trials, participants are divided into at least two groups: the group receiving the new vaccine (study group) and the group receiving a placebo (i.e., an inactive substance) or an already registered vaccine (control group). During the trial, individual participants and trial staff do not know to which group a participant belongs. The data for the study and control groups are compared to help determine the effectiveness of the vaccine versus an already licensed vaccine or a placebo. The groups of participants and the procedures followed for each group during the trial are another important part of the design of the trial.

Once the design (the study protocol) has been completed, it is submitted to a review board for evaluation of safety and ethical considerations. The study protocol is created to safeguard the health of the participants and to answer specific research questions about the product. After reviewing the protocol, the review board has the final say

in whether a clinical trial can take place. In addition to its review prior to the start of clinical trials, the review board conducts periodic evaluations throughout the length of the trial in order to make sure that safety and ethical standards are being met. Many trials, particularly AIDS vaccine trials, have community advisory boards that evaluate the study protocol to ensure that the community's culture and other community-specific concerns are taken into consideration. Community advisory boards could also participate in monitoring trials and educating community members, among other interested groups. In addition to the review board and community advisory board, the clinical trial may be filed with the proper regulatory agency and/or national clinical trial registry for review prior to the start of the study.

WHO PARTICIPATES IN A CLINICAL TRIAL?

Trial volunteers range from healthy adults in Phase 1 to product users in Phase 4, with each phase including a different set of participants. Clinical trial participants are selected based on guidelines to ensure that the vaccine is evaluated in the correct population. These guidelines include age range, location, and health status of the participant, among others, and they depend on the intended use of the vaccine candidate. In all cases, local trial site staff, typically coordinators and/or nurses, make certain participants are informed about the study, including its purpose, duration, required procedures, and key contacts. Researchers are obligated to provide potential volunteers the information they need to make an informed decision on whether to participate in the clinical trial. When trial staff are not conversant in a volunteer's language, translators are made available to provide the information and answer questions.

Often the community surrounding the research institution conducting the trial has a great interest in the trial, since community members are often participants. Communities want to understand if there are risks to the trial and if the community will have access to the vaccine if it is shown to be safe and effective. Interactions with the community and other local stakeholders includes sharing background information about the disease, the vaccine candidate and manufacturer, risks, benefits, how the clinical trial is being conducted, and what organizations are collaborating on the trial.

WHAT ABOUT SAFETY?

Safety is the priority of the entire clinical trial process. It is for this reason that researchers first test the vaccine in preclinical studies in laboratories and animals. The clinical studies begin with a small number of healthy adults in Phase 1 trials. If the data from Phase 1 trials are encouraging, the manufacturer proceeds to test the vaccine in those for whom it is intended, for example, young children. If a vaccine is designed for use in children,

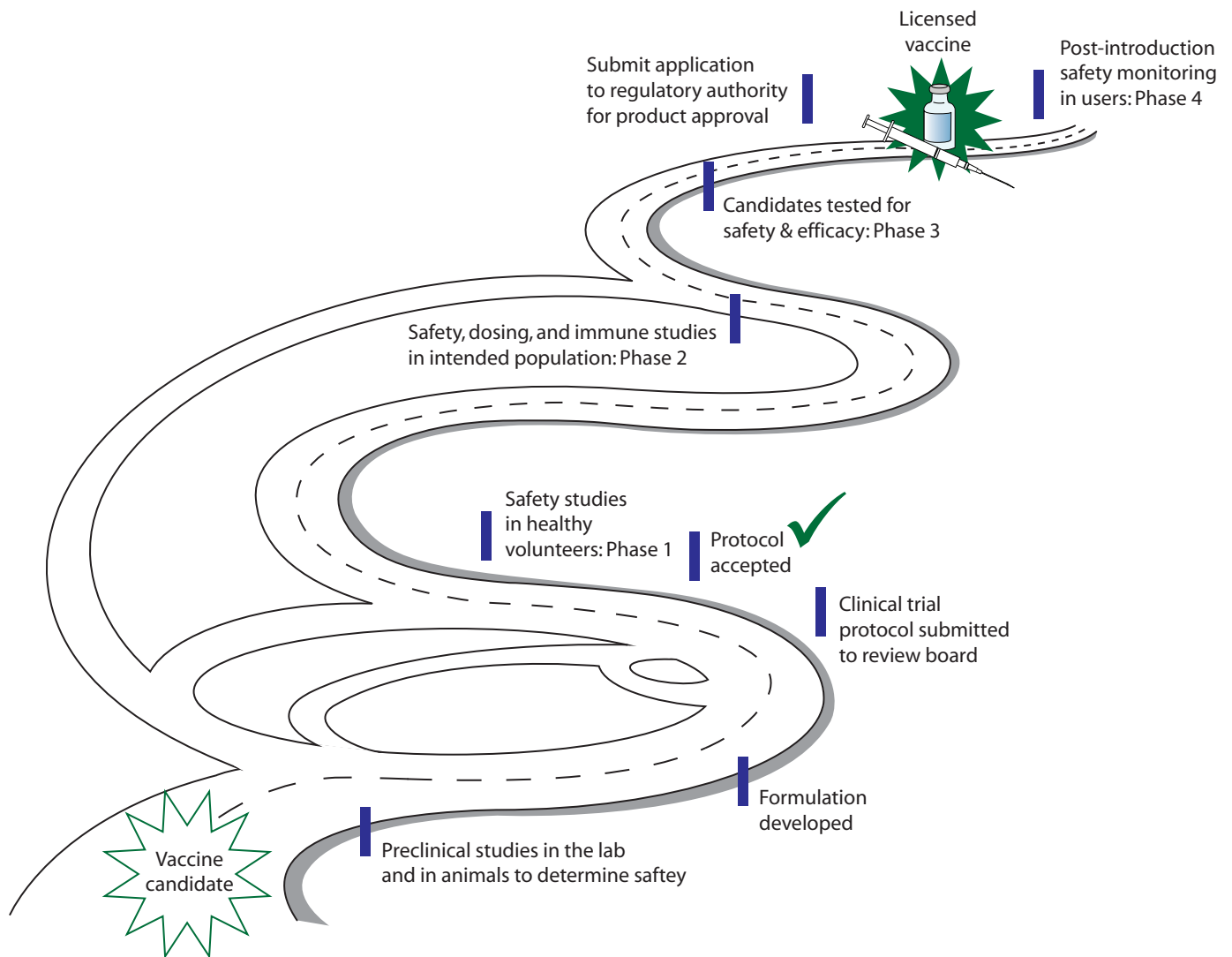
Phase 2 studies generally include sequenced testing of the vaccine, first in adults and adolescents, then in children (2 to 5 years), toddlers (12 to 23 months), and finally infants (2 to 12 months). Descending-age studies are important because infants have developing immune systems. Further positive results from Phase 2 trials lead to testing the product in a larger number of people to determine the vaccine's ability to protect against the disease (Phase 3 trials). Finally, safety monitoring (Phase 4) studies are conducted, in conjunction with product licensure, to determine any additional information, such as risk, benefit, and optimal use.

Overview of Clinical Trial Phases

Trial Phase	Number of Participants*	Duration	Purpose
Phase 1	20-100	30-180 days	Safety
Phase 2	20-300	30-180 days	Safety, dosing, and immune response
Phase 3	500-50,000	1 month-3 years	Efficacy and safety
Phase 4	Several thousand	Years	Post-introduction monitoring, safety

* The number of participants and the duration of each phase of clinical trials may vary based on the product being tested and the population and location of the trial.

Throughout the clinical trial phases, researchers and medical staff conduct regular follow-up to monitor the health of volunteers and identify any potential safety issues as quickly as possible. In addition to institutional review boards (IRB) who approve the study protocol and conduct periodic monitoring of the trials, data and safety monitoring boards (DSMB) assess the safety of the product in the participants independently from the IRB. Recommendations of the DSMB are required to proceed further with the trial (e.g., into a younger age group) and are another layer of safety monitoring and review present in clinical studies. These review boards not only provide the go-ahead for clinical trials but can also stop trials. For example, if a product shows great benefit to the study group while the control group (those receiving a placebo or currently available treatment) is either unprotected or partially protected, review boards may stop the trial because it is unethical not to give the new product to the control group. Additionally, trials may be stopped because of adverse events, or side effects, from the product being tested. In this case, review boards may stop the trial if the adverse event poses the risk of endangering the trial participants.



WHY ARE CLINICAL TRIALS IMPORTANT?

Clinical trials are a critical part of the vaccine development process. For new vaccines to reach those most in need, they must be licensed by a regulatory agency, which requires the product to have been thoroughly tested in the intended recipients. Regulatory officials review the results of clinical trials to decide whether to license a vaccine and who should receive it. Clinical trials are an important step in making new vaccines available against life-threatening diseases.

PATH is working to close gaps in access to lifesaving vaccines. By strengthening health systems, expanding access to new vaccines, accelerating research and

development, and creating innovative technology solutions, PATH is working to make safe and effective vaccines affordable and available to those most in need.

RESOURCES

- International AIDS Vaccine Initiative. VAX: <http://www.vaxreport.org/Pages/default.aspx>
- US Food and Drug Administration. Clinical Trials: <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
- US National Institutes of Health. Department of Health and Human Services. An Introduction to Clinical Trials: <https://www.clinicaltrials.gov/ct2/about-studies>



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455 Massachusetts Ave NW,
Suite 1000
Washington, DC 20001