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Clinical Trials Knowhows for Novel Vaccine Development

Deepanker Bisht[1], Samriddhi Dubey[2]

[1]Phd Scholar, Division of Veterinary Biotechnology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh (Corresponding Author)

[2]Veterinary Virologist, Research and Development Laboratory, SPF's Division, Venky's India Private Limited, Pune, Maharashtra

Abstract: ***Vaccination, by saving millions of lives, is unquestionably one of the biggest triumphs in the history of medicine. Numerous efforts and substantial amount of research are focused on producing an efficacious and qualified vaccine for the current pandemic of COVID-19. Leading pharmaceutical companies have started promising clinical trials worldwide recruiting healthy human volunteers to contribute and become a partner in scientific discovery. The clinical trials process includes human studies for acceptable safety and reactogenicity of a potential vaccine in Phase I trial and ensuring the proof-of-concept of the vaccine in Phase II. The final step in clinical evaluation is Phase III trial intended to provide a conclusion needed for license and marketing approval. We, in this article, have tried to address the clinical trials and evaluation process required to define the safety profile, monitoring, licensing and approval of a new vaccine candidate.***

Keywords: Clinical trials, vaccine, human volunteers, COVID-19

1. Introduction

Clinical trials are research studies that include new tests and treatments and evaluate their effects on human health. They are the primary way for researchers to find out whether a new treatment, a new vaccine, a drug or diet or a medical device is safe and effective in people. A clinical trial is often used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment. Clinical trials are conducted only when satisfactory information has been gathered on the quality of the non-clinical safety and health authority/ethics committee approval is granted in the country where the approval of the drug is sought. A novel vaccine candidate undergoes an elaborate development process after discovery. Regulatory agencies like European Medicine Agency, World Health Organization and United States Food and Drug Administration divide this development process into preclinical (*in vitro* and *in vivo* testing in animals) and clinical (clinical trials in human subjects) stages. Though there are common principles to guide the development of any vaccine candidate, but each vaccine follows a unique development path depending on characteristics such as the type of vaccine (live/killed/subunit/DNA/peptide), disease epidemiology, target population and the availability of a pre-existing vaccine. Vaccine testing and trial is a four stage process: animal testing that involve proper antigen to invoke an immune response, phase I clinical testing on a small human study group to determine its safety and the immune response it provokes, extended safety trials in phase II followed by phase III testing on thousands of people to confirm efficacy. With the emergence of the current earth-shaking pandemic COVID-19, many countries worldwide are battling and competing to release the first effective vaccine against the causative agent SARS CoV2. At present, 140 vaccine candidates are in pre-clinical trial stage and 23 have entered the clinical evaluation stage according to World Health Organization. India, often referred as pharmacy of the world, have seven pharmaceutical companies viz. Bharat Biotech, Serum Institute, Zydus Cadila, Panacea Biotec, Indian Immunologicals, Mynvax and Biological E working rigorously in the direction of developing a vaccine against the viral disease.

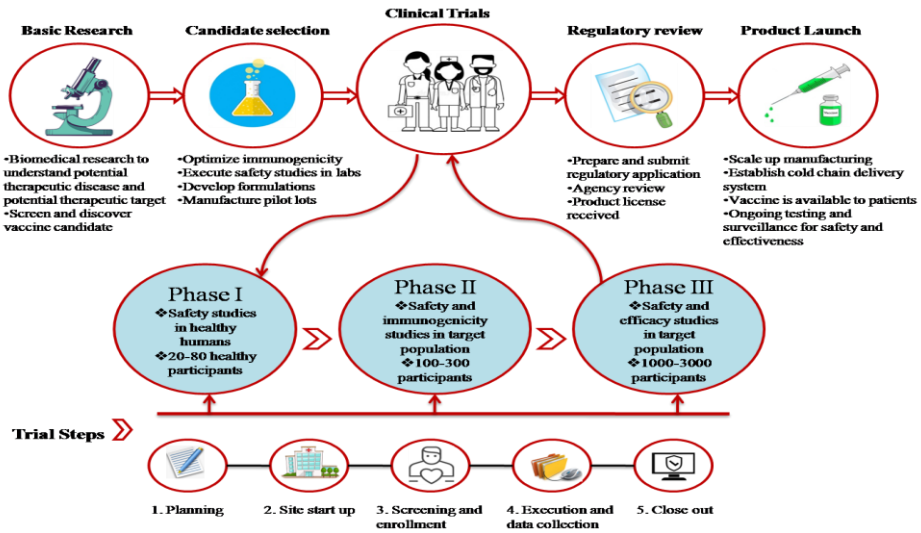

Figure 1: The process of vaccine development

Participation and Protection in Clinical Trials

Vaccines are indispensable for the prevention of viral diseases. The testing procedures for vaccines unlike drugs require healthy volunteers. To ensure the health and eligibility of participants in these studies, a screening is conducted before the start of the study. This screening is conducted according to a research protocol and involves medical history, physical examination, blood test etc. In some cases blood is tested for viral DNA or RNA and samples like urine, stool and nasopharyngeal wash secretions may be tested for viruses or antibodies to the virus. Additional screening in the form of electrocardiogram (ECG), chest radiograph (CXR) and pulmonary function tests (PFTs) is performed with the storage of samples for future research. This helps to put forth the standards and identification of group of human volunteers outlining their eligibility criteria to participate in investigational vaccine trials or challenge studies conducted by companies. The qualifying factors for participants in a clinical study are called inclusion criteria and are based on some characteristics like age, gender, availability to participate for the planned duration of the clinical trial, ability and willingness to complete the informed consent process and finally to become a part of procedures as needed for screening process. The factors that preclude someone from participating are called exclusion criteria and are based on previous treatment history and medical conditions that significantly alter the immune system or could interfere with the subject participating and completing the study. The clinical development for vaccines involves a step-down approach where safety is first tested in adults followed by children and infants at last.

All the information about a clinical study is provided to potential and enrolled participants by the researchers through a process called informed consent. The provided information helps people decide whether they want to join and continue to participate in the study. The process of informed consent is engaged to protect volunteers and should provide sufficient information to a person about the risks involved as well as potential benefits of the study. The process may involve question and answer sessions, instructions and activities to calculate the participants understanding. Participants may withdraw at any time even if the study is not over. In India, each conducted clinical study or trial of a vaccine regulated by WHO guidelines must be approved and regulated by NRAI (National Regulatory Authority of India) which is a pre-requisite for WHO prequalification of vaccine. NRAI comprises of the Central Drugs Standard Control Organisation (CDSCO), State Drug Regulatory Authorities, Adverse Events Following Immunization (AEFI) and Pharmaco-vigilance Programme of India (PvPI). These authorities maintains an Institutional Review Board (IRB) which consists of doctors, researchers and members of the community making sure that the study is ethical and that the rights and well-being of participants are protected.

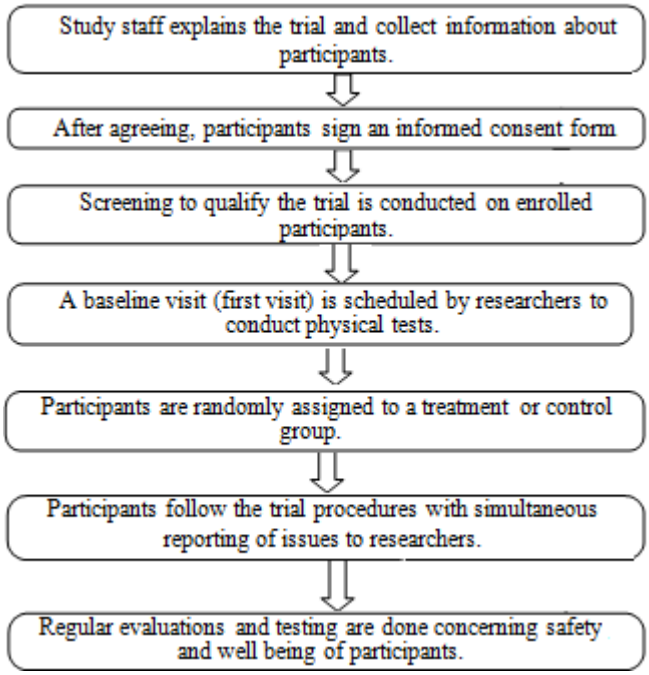

Figure 2: A basic workflow of events during a clinical trial process

Phases of Clinical Trials

Before a regulatory approval, the potential vaccine candidate undergoes three phases of development that progress sequentially: Phase I, Phase II and Phase III. After successful fruition of Phase III trials and following licensure of the product, Phase IV studies, also referred to as post marketing surveillance studies (PMS) are used to keep track of vaccine safety and effectiveness in the population.

Phase I Trial

First-in-man Phase I studies refer to the first administration of a potential vaccine candidate in humans involving a small group of adults, usually between 20-80 subjects. The subjects should be healthy and immunocompetent adults who are at minimum risk of acquiring a vaccine-relevant infection predetermined by serology and exposure. These trials may be non-randomized and open label in which the researchers and subjects know whether a vaccine or placebo is used. The purpose of Phase I testing is to evaluate the safety, reactogenicity and to determine the type and extent of immune response. Sometimes dose, mode of vaccine and immunization schedule is also assessed. Phase I trial site should be located within or near a tertiary care hospital so that volunteers undergo intensive investigations in closely monitored clinical settings. Tolerability and reactogenicity caused due to the vaccine or the process of vaccination are majorly evaluated in a Phase I study. A successful Phase I trial will proceed to Phase II clinical evaluation.

Phase II Trial

Phase II studies recruit hundreds to thousands of individuals and are expected to provide a clinically meaningful outcome and efficacy end points. Phase II trials are conducted to identify the vaccine preparation, optimal dose, qualitative aspects of immune response, schedule of immunization and route of administration. The studies follow statistically randomized control designs and are mostly conducted in community-based sites where information about the

population and pathogen/disease of interest is available. Phase II trials can also provide primary information on protective efficacy through human challenge trials, wherein healthy volunteers are deliberately infected with the pathogen. Such challenge studies are only performed for selected diseases wherever it is scientifically and ethically justified where complete and successful cure can be obtained. Phase II trials offer rapid assessment of the usefulness of a vaccine candidate in a limited number of subjects and thus allow quicker vaccine development and serves as stringent go/no-go step for progressive development.

Phase III Trial

Successful Phase II qualified vaccine candidates are put to large scale clinical trials called Phase III trials enrolling thousands of subjects from the target population. Pivotal Phase III studies are conducted in field conditions similar to future use and are typically designed to evaluate efficacy and safety prior to registration and approval to market. Phase III tests are randomized and double blind where participants are randomly allocated to receive either the experimental or control vaccine (may be a placebo, a saline solution, different vaccine or nothing). Sometimes certain rare side effects might not surface in low incidence like in smaller groups in earlier phases. In such cases, larger study population is employed to detect a significant difference. If the Phase III results demonstrate safety and efficacy, the vaccine manufacturer will submit a Biologics License Application to the national regulatory authority. The authority will inspect the manufacturing facility, review and monitor the production of vaccine followed by approval for licensure of the vaccine.

2. Conclusion

Physicians, researchers and pharmaceutical companies are working tirelessly to develop an effective preventative vaccine and therapeutic strategies against the emerging pandemic phenomenon of COVID-19. Lessons from earlier lethal viral diseases like SARS and Ebola have prepared laboratories to attempt tailoring a vaccine in a short span and bring them to clinical study platforms as a public health priority. The most important and difficult challenge for the future vaccine is proof of clinical safety for which validated and extremely supervised clinical trials need to be conducted. Undoubtedly, the integration of multidisciplinary knowledge with efficient vaccine development strategies and streamlining of regulatory approval processes may facilitate this trend.

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