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CLINICAL TRIALS PROCESS OF COVID-19 VACCINES: A COMPREHENSIVE OVERVIEW

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ABSTRACT

The COVID-19 pandemic has sparked an extraordinary worldwide reaction, including scientific trials to develop viable therapies, vaccinations, and prevention measures. This abstract gives a complete explanation of the clinical trial process for COVID-19. It describes the major steps in conducting clinical trials, such as research design, participant recruiting, informed consent, data collecting, analysis, and reporting. Various forms of clinical trials, including randomised controlled trials, observational studies, and adaptive trials, are reviewed, along with their benefits and drawbacks. Furthermore, ethical considerations and regulatory requirements for COVID-19 clinical studies are discussed. The importance of collaboration among researchers, healthcare providers, regulatory agencies, and pharmaceutical corporations in accelerating the clinical trial process is highlighted.

KEYWORDS: Clinical trials, Regulatory body, Healthcare, Phases.

INTRODUCTION

Research on novel diagnostic procedures and therapeutic approaches that assess their impact on human health outcomes is known as clinical trials.[1]

A clinical trial is a type of research study that determines whether a novel medical intervention or an innovative approach to an already-existing treatment would be more effective to prevent and screen for diagnosis or treat a disease.[2]

Clinical trials are biomedical or health-related research investigations conducted on humans according to a predetermined protocol. In order to evaluate medications, stem cells, and other

biological products, surgical techniques, radiological techniques, equipment, behavioural therapies, and preventive care, people volunteer to participate in clinical trials. This comprises one of the major concerns that are adequately addressed in a study, the funding institutions, the institutions where the research takes place, and regulatory agencies have developed regulations and guidelines for conducting human research.[4]

COVAXIN CLINICAL TRIALS

❖ PHASE 1

- In a Phase 1 placebo-controlled, double-blinded clinical trial, an inactivated SARS-CoV-2 vaccine (BBV152) was evaluated in 375 subjects.
- On day 28 (14 days after 2nd dose), all subjects who received the vaccine intramuscularly had significantly elevated Spike binding IgG antibodies and Neutralizing Antibody titers.
- The vaccine induced antibody responses reported, were able to neutralize both homologous (vaccine virus strain) and heterologous (divergent) SARS-CoV-2 strains.
- A Th1 biased T-cell response was observed.
- Following vaccination, systemic and local responses were often modest and temporarily resolved. There were no documented major (grade 3-4) adverse effects.

❖ PHASE 2

- In a double-blind, randomised, multi-centre, phase 2 clinical trial a total of 380 healthy children and adults were randomised to receive two vaccine formulations (n=190 each) with 3 µg and 6 µg with Algel-IMDG.
- Two intramuscular doses of vaccines were administered (four weeks apart).
- Three months (at day 104) following the second vaccination, BBV152 produced significant levels of neutralising antibodies that remained increased in all subjects in a follow-up of the phase 1 trial. Based on these results, we hypothesize that BBV152 can generate antibodies that may persist for 6-12 months.
- In comparison to the phase 1 trial, higher neutralising titres (2-fold) were noted in the phase 2 investigation. More Th1-biased cytokines than Th2-biased cytokines were induced by both vaccination groups.
- After receiving two doses, both vaccination groups experienced very few systemic and local adverse responses, most of which went away 24 hours after they started. In this trial, no significant adverse events were recorded.

❖ **PHASE 3**

- 25,800 persons between the ages of 18 and 98 were included in the Phase 3 study; 2,433 of these patients were over 60, and 4,500 had comorbidities.
- For adult participants who were serologically negative for SARS-CoV-2 at baseline, the primary endpoint of the Phase 3 clinical trial is the first instance of PCR-confirmed symptomatic (mild, moderate, or severe) COVID-19 with onset at least 14 days following the second study immunisation.
- Based on 43 cases, the first interim analysis yielded a point estimate of 80.6% vaccination efficacy: 36 cases of COVID-19 were observed in the placebo group and 7 cases in the BBV152 (COVAXIN®) group.
- Preliminary examination of the safety database, which was part of the interim study, revealed that severe, serious, and medically attended adverse events were rare and evenly distributed across vaccine and placebo groups. The experiment is being managed by IQVIA and is being conducted in accordance with Good Clinical Practice guidelines. Data from 25,800 participants, received vaccine or placebo in a 1:1 ratio showed that the vaccine candidate was well tolerated.
- COVAXIN® demonstrated 81% interim efficacy in preventing COVID-19 in those without prior infection after the second dose.

COVISHIELD (ASTRAZENECA) CLINICAL TRIALS

❖ **PHASE 1**

Methods

- Four ongoing blinded, randomised, controlled studies conducted in the UK, Brazil, and South Africa are included in this analysis. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline).
- A fraction in the UK study received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort The ChAdOx1 nCoV-19 group's participants were given two doses (standard dose; SD/SD cohort) that contained 5×1010 virus particles.
- Participants were analysed based on therapy received, with data cutoff on Nov 4, 2020.
- Symptomatic COVID-19 in seronegative individuals with a positive swab from a nucleic acid amplification test more than 14 days after a second vaccination dose were included

in the primary efficacy analysis. In order to determine vaccine efficacy, a robust Poisson regression model that was age-adjusted was used, and the result was 1 - relative risk.

- The studies are registered at NCT04324606, NCT04400838, NCT04444674, ClinicalTrials.gov, and ISRCTN89951424.[38]

Findings

23 848 people were enrolled between April 23 and November 4, 2020, and 11 636 participants (4088 in Brazil and 7548 in the UK) were included in the interim primary efficacy analysis. In the ChAdOx1 nCoV-19 group, the vaccine's efficacy was 62·1% (95% CI 41·0–75·7; 27 [0·6%] of 4440 vs. 71 [1·6%] of 4455 in the control group) in participants who received two standard doses, and 90·0% (67·4–97·0; three [0·2%] of 1367 vs 30 [2·2%] of 1374; pinteraction=0·010) in those who received a low dose and then a standard dose. Between the two groups, the overall vaccine effectiveness was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 versus 101 [1·7%] of 5829). Ten COVID-19 instances were hospitalised starting 21 days after the first dosage; all of these cases were in the control arm. Of those, two were classed as severe cases, one of which resulted in death. Safety follow-up lasted 74 341 person-months (median 3·4 months, IQR 1·3–4·8): 168 patients experienced 175 severe adverse events, with 84 occurring in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events—one in the ChAdOx1 nCoV-19 group, one in the control group, and one involving a person whose identity is yet unknown—were flagged as potentially vaccine-related.[38]

❖ **PHASE 2/3**

Methods

- In this report of the phase 2 component of a single-blind, randomised, controlled, phase 2/3 trial (COV002), healthy adults aged 18 years and older were enrolled at two UK clinical research institutions into immunogenicity subgroups based on age: 18–55 years, 56–69 years, and 70 years and older.
- Individuals who did not have significant or uncontrolled medical comorbidities or, if older than 65, a high frailty score, were eligible.
- The individuals were first drawn from a low-dose cohort. Then, within each age group, they were assigned at random to receive either a control or intramuscular ChAdOx1 nCoV-19 ($2{\cdot}2 \times 1010$ virus particles).vaccine, MenACWY, using block randomisation and stratified by age and dose group and study site, using the following ratios: in the 18–

55 years group, 1:1 to either two doses of One dosage of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; in the 56–69 years old group, 3:1:3:1. doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. The interval between prime-booster regimens was 28 days.

- Participants were then recruited to the standard-dose cohort (3·5–6·5 × 1010 virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY.
- Participants and researchers were blind to the vaccination distribution, but not the personnel giving the shot.
- This report's particular goals were to evaluate the safety and humoral and cellular immunogenicity of a single-dose and two-dose regimen in persons over the age of fifty-five.
- Humoral responses were measured using a live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microneutralization assay (MNA80), a multiplex immunoassay, and an internal standardised ELISA up to a year following the booster shot.
- Through the use of an ex-vivo IFN-γ enzyme-linked immunospot test, cellular responses were evaluated. The trial's coprimary outcomes were safety, as determined by the incidence of major adverse events, and efficacy, as determined by the number of cases with symptomatic, virologically confirmed COVID-19.
- Analyses were by group allocation in participants who received the vaccine.[39]

Findings

Between May 30 and August 8, 2020, 560 participants were enrolled: 160 were between the ages of 18 and 55 (100 were assigned to ChAdOx1 nCoV-19, 60 to MenACWY), 160 were between the ages of 56 and 69 (120 were assigned to ChAdOx1 nCoV-19: 40 to MenACWY), and 240 were over the age of 70 (200 were assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY). Three participants' poorly labelled samples prevented them from being included in immunogenicity analyses, seven participants did not receive the boost dosage of their prescribed two-dose regimen, and one person received the wrong vaccination. 280 (50%) of 552 analysable participants were female. Participants who received ChAdOx1 nCoV-19 were more likely to experience local and systemic reactions than those who

received the control vaccine. These reactions were similar to those that have been previously reported, including injection-site pain, fever, headaches, and muscle aches, but they were less common in older adults (aged ≥56) than in younger adults. Following the initial vaccination with two standard doses of ChAdOx1 nCoV-19, 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 participants in the 56–69 years group, and 30 (61%) of 49 participants in the 70 years and older group reported local reactions; 42 (86%) of 49 participants in the 18–55 years group, 23 (77%) of 30 participants in the 56–69 years group, and 32 (65%) in the 70 years and older group reported systemic reactions. Thirteen major adverse events occurred during the trial period as of October 26, 2020, and none of them were thought to be connected to either study vaccination. Across the three age cohorts (standard-dose groups: median anti-spike SARS-CoV-2 IgG responses 28 days following the boost dose) among individuals who received two doses of the vaccine,: 18–55 years, n = 39; 56–69 years, n = 26; ≥70 years, n = 47; p = 0·68; 20 713 arbitrary units [AU]/mL [IQR 13 898–33 550], n = 39; and ≥70 years, n = 16 170 AU/mL [10 233–40 353]. After receiving a boost dose, all age groups displayed the same neutralising antibody titres (median MNA80 at day 42 in the standard-dose groups: n = 39 for ages 18–55, 193 [IQR 113–238], n = 20 for ages 56–69, 144 [119–347], n = 20, and n = 47 for ages 70 and beyond, 161 [73–323], p = 0·40).208 (>99%) of the 209 boosted subjects developed neutralising antibody responses by the 14-day mark following the boost dosage. After receiving a single standard dosage of ChAdOx1 nCoV-19, T-cell responses peaked on day 14. Between the ages of 18 and 55, the median number of spot-forming cells (SFCs) per million peripheral blood mononuclear cells (IQR 841–2428) was 1187 (n = 24); between 56 and 69, the number was 797 (n = 29), and between 70 and older, the number was 977 (n = 48).[39]

PFIZER CLINICAL TRIALS

❖ PHASE 1

- In the United States, two lipid nanoparticle-formulated, nucleoside-modified RNA vaccine candidates were randomly assigned to receive either a placebo or one of two RNA vaccine candidates. BNT162b1 encodes a secreted trimerized SARS-CoV-2 receptor-binding domain, while BNT162b2 encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilised in the prefusion conformation. The trial was a placebo-controlled, observer-blinded, dose-escalation, phase 1 trial.
- Immunogenicity was the secondary outcome, with safety (such as local and systemic reactions and adverse events) being the primary concern.

- The vaccine candidate, participant age, and vaccination dose level (10 µg, 20 µg, 30 µg, and 100 µg) were used to determine the trial groups. All subjects got two doses, separated by 21 days, with the exception of one group, which received a single dosage of 100 µg of BNT162b1.
- A total of 195 participants underwent randomization. Of the fifteen individuals in each of the thirteen groups, twelve received the vaccination and three received a placebo.
- Compared to BNT162b1, BNT162b2 was linked to a decreased incidence and severity of systemic responses, especially in older persons. The two vaccine candidates produced dose-dependent SARS-CoV-2–neutralizing geometric mean titers in both younger and older people that were on par with or greater than the geometric mean titer of a panel of serum samples from convalescent SARS-CoV-2 patients.

❖ **PHASE 2**

- In the phase 2/3 evaluable efficacy data submitted to the FDA, the Pfizer trials' population includes 37,796 patients, of whom 37,088 (98.1%) completed the two-dose regimen of either BNT162b2 or placebo (split 1:1). Merely thirteen patients had withdrew from evaluation because of an adverse event at the time of EUA submission.
- The evaluable population observed for vaccine efficacy included 49.4% females, 81.9% white participants, 9.8% African American participants, 4.4% Asian participants, and <3% from other racial groups. 21.4% of participants were over 65, while another 26.2% were of Hispanic or Latino heritage.
- The average age of the participants was 51 years, and the most common comorbidities that were recorded were lung disorders (7.8%), diabetes (8.4%), and obesity (35.1%).More than three-fourths (76.7%) of participants were from the US.
- Overall, comorbidities were reported in 46.2% of all observed patients. Of the patients treated with BNT162b2, only 545 exhibited baseline signs of prior SARS-CoV-2 infection.
- Trial goals
- A primary endpoint of BNT162b2 vaccination effectiveness against proven COVID-19 was sought by the investigators in individuals who did not exhibit any prior signs of SARS-CoV-2 infection before seven days following the second dose.
- The candidate's vaccination effectiveness against proven COVID-19 in individuals with and without such prior infection evidence was the second primary efficacy goal. Since the

suggested time for developing immunity is seven days following dosage two, the investigators counted cases starting from that point for both objectives.

Findings

- The total vaccine effectiveness against proven COVID-19 at least 7 days after their second dose of BNT162b2 was 95% (95% CI, 90.3 – 97.6) among participants who had not previously contracted SARS-CoV-2 before 7 days after their second dose. Investigators observed just 8 COVID-19 cases in the treatment group, versus 162 cases in the placebo group.
- In the second primary endpoint including participants with and without prior SARS-CoV-2 infection before and during vaccination regimen, vaccine efficacy at least 7 days after dose 2 was 94.6% (95% CI, 89.9-97.3). Once more, there was a significant difference in the rate of COVID-19 instances between vaccinated patients (n = 9) and placebo-treated individuals (n = 169).
- In subgroup analysis, the vaccine was linked to a 95.4% efficacy among people at risk of COVID-19 severity (95% CI, 87.8-98.8). "At risk" is defined as having at least one item on the Cahrlson comorbidity index or a body mass index (BMI) of ≥30, suggesting obesity. Though the population was too small to perceive absolute interpretability, at-risk participants aged ≥65 years were associated with a 91.7% vaccine efficacy (95% CI, 44.2-99.8).
- Just 4 subjects showed signs of severe COVID-19 instances, the primary secondary objective, ≥7 days after the second treatment. Only one of them had been given BNT162b2. Nevertheless, the FDA pointed out that the patient did not have risk indicators for a severe illness, was not hospitalised, and had oxygen saturation levels of 93% during the clinical visit, which led to the participant's serious diagnosis.
- Within the phase 2/3 safety population, researchers did find that a higher percentage of vaccine recipients than placebo recipients reported adverse events. This difference was primarily due to both solicited adverse events that occurred within the first seven days after vaccination and unsolicited adverse events that were associated with reactogenicity symptoms in participants who were not part of the reactogenicity subset in the trial.That said, investigators observed a balance of rates of serious adverse events, deaths, and trial withdrawals among the treatment groups.
- Injection site pain was the most commonly reported occurrence in terms of solicited local reactions among participants who were 18 years of age or older; it was more commonly

reported in younger patients following the second dosage of BNT162b2, and it was generally classified as moderate. Participants reported injection site swelling and redness considerably less frequently, and this was true for all age groups.

- Younger patients also had a higher frequency of requested systemic events, such as fever, exhaustion, headache, chills, vomiting, diarrhoea, and new or worsening muscle/joint pain. After dose 2, participants as a whole had more frequent and severe systemic adverse effects.
- The most frequent occurrences across all age categories were headache, weariness, and new or worsening muscle discomfort.
- In relation to unintentional, non-serious side effects, researchers found that vaccinated patients had a higher incidence of lymphadenopathy (n = 64) compared to placebo (n = 6), and there were also 4 incidences of Bell's palsy among the vaccinated population.
- Moreover, researchers noted three vaccine-related major adverse events in the BNT162b2 group: lymphadenopathy, cardiac arrhythmia, and shoulder damage. Two of the trial's six participants who passed away were those who received the vaccination. Three days after the second dose, one patient went into cardiac arrest and died; three days after the first dose, the other patient passed away from arteriosclerosis.
- The Federal Drug Administration stated that all deaths "represent events that occur in the general population of the age groups where they occurred, at a similar rate."
- Finally, no particular safety concerns were raised by the investigators in relation to participant age, race, ethnicity, medical comorbidities, or history of SARS-CoV-2 infection. Results from pregnancy are unknown aside from a few unintentional adverse events that occurred in the placebo group and only included 23 female participants up until the trial's November 14 cutoff date.

❖ **PHASE 3**

- Participants 16 years of age or older were randomly assigned in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose), in a pivotal effectiveness trial that was observer-blinded and placebo-controlled. The vaccine's effectiveness against laboratory-confirmed Covid-19 and safety were the main outcomes.
- 43,548 individuals in all were randomly assigned, and 43,448 of them got injections: 21,720 with BNT162b2 and 21,728 with placebo.

- Those who received BNT162b2 had 8 cases of Covid-19 with onset at least 7 days after the second dose, while those who received a placebo had 162 cases.; BNT162b2 was 95% efficient at preventing Covid-19 (95% reasonable interval, 90.3–97.6).
- Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions.
- Nine of the ten occurrences of severe Covid-19 that started after the first dose happened in receivers of placebos, and one involved BNT162b2.
- BNT162b2's safety profile included headache, weariness, and mild-to-moderate injection-site soreness that subsided quickly. Serious side effects were uncommon and comparable in the vaccination and placebo groups.
- 28 days following the initial dosage, primary efficacy analysis shows that BNT162b2 is 95% effective against COVID-19; 170 confirmed instances of the virus were assessed, with 162 cases observed in the vaccine group (eight) and the placebo group (ten).
- Across age, gender, race, and ethnicity demographics, efficacy was constant; over 94% of persons over 65 showed efficacy.
- The United States Food and Drug Administration (FDA) has required safety data milestones for Emergency Use Authorization (EUA) and they have been met. The data show that the vaccine was well tolerated across all populations, with over 43,000 participants enrolled; no serious safety concerns were noted, and the only Grade 3 adverse event that occurred more frequently than 2% of the time was fatigue (3.8%) and headache (2.0%).
- Businesses intend to share data with other regulatory bodies worldwide and file an EUA to the FDA in a matter of days. They also anticipate producing up to 50 million vaccine doses globally in 2020 and 1.3 billion doses by the end of 2021.

JOHNSON AND JOHNSON

❖ **PHASE 1 & 2a**

METHODS

We randomly assigned healthy adults between the ages of 18 and 55 (cohort 1) and 65 years or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5×1010 viral particles (low dose) or 1×1011 viral particles (high dose) per millilitre, or placebo in a single-dose or two-dose schedule in this multicenter, placebo-controlled, phase 1–2a trial. Cohort 2 is gathering longer-term data comparing a single-dose regimen with a two-dose regimen; those

findings are not presented here. The safety and reactogenicity of each dosing schedule served as the main objectives. Cohort 2 is gathering longer-term data comparing a single-dose regimen with a two-dose regimen; those findings are not presented here. The primary end points were the safety and reactogenicity of each dose schedule.[40]

RESULTS

The most commonly requested adverse effects following the administration of the first vaccination dose in 805 participants in cohorts 1 and 3, as well as following the second dose in cohort 1, were myalgia, exhaustion, headaches, and injection site discomfort. Fever was the most common systemic adverse effect. Compared to cohort 1, cohort 3 showed a lower frequency of systemic adverse effects, as did individuals who received a lower dosage of the vaccination compared to those who received a higher dose. Reactogenicity was lower after the second dose. Regardless of vaccine dosage or age group, neutralizing-antibody titers against the wild-type virus were found in 90% or more of all participants on day 29 following the first dose (geometric mean titer [GMT], 212 to 354), and they increased further to 288 to 488 in cohort 1a to reach 96% by day 57. Titers didn't change until day 71 at the latest. The titer increased by a factor of 2.6 to 2.9 (GMT, 827 to 1266) with a second dosage. Neutralising antibody responses and spike-binding antibody responses were comparable. Day 15 results showed that 76–83% of cohort 1 individuals and 60–67% of cohort 3 participants had CD4+ T-cell responses, with a distinct preference for type 1 helper T cells. While overall CD8+ T-cell responses were strong, they were lower in cohort 3.[40]

SUMMARY

The drug development life cycle is vital to delivering safe and effective drugs. Although there are favourable treatments and therapies in the pharmaceutical supply chain, there is a significant need for new drugs, especially during the COVID-19 pandemic.

But the ability to quickly develop and deploy medications is difficult because the drug development life cycle is long and complex, taking 10 to 15 years to develop a product.

The FDA states that there are five steps in the medication development process.

i. The first step is discovery and development. In this step, In order to create a product that will halt the consequences of the sickness, researchers investigate fresh perspectives into the disease process in this step. Then, they test molecular compounds to find possible beneficial effects against certain diseases.

- Researchers discover new drugs through existing treatments and new technologies as well. Then, they conduct experiments to gather information on how the drug is absorbed, distributed, metabolized, and excreted.
- They also discover its potential benefits and mechanisms of action, the best dosage, the best way to give the drugs, side effects of adverse events, how it affects different groups of people, how it interacts with other drugs and treatments, and its effectiveness compared to other drugs.

ii. The second step in the drug development process is preclinical research, which includes in vitro and in vivo trials

- In the preclinical research step, drugs go through laboratory and animal testing to answer basic questions about safety.
- In this step, researchers to use laboratory best practices as defined in medical product development regulation to test safety.
- These regulations include study conduct, personnel, facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight for each study.

iii. The third step is clinical research. This refers to studies or trial that are done in people

- Through clinical research, specific questions related to a medical product are answered. Through these answers, researchers decide who qualifies to participate, how many people will be apart of the study, how long the study will last, a control group, how the drug will be administered, what assessments will be conducted, and how the data will be reviewed.
- Clinical trials consists of 4 phases:

a. Phase 1: This phase aims to figure out the highest dose humans can take without serious side effects. During this phase, participants are intensively observed by investigators to observe how their bodies respond to the medicine.

b. Phase 2: Investigators monitor participants for several months or years to see how effective the medication is and to gather more information about any side effects it might cause.

c. Phase 3: The purpose of phase III is to evaluate how the new medication works in comparison to existing medications for the same condition. The drug must be shown to be at least as safe and effective as current treatment choices in order for the trial to proceed.

iv. Phase 4: Phase IV clinical trials take place following a drug's FDA approval. This stage can go on for years and involves thousands of participants. This stage is used by investigators to learn more about the long-term safety, efficacy, and potential advantages of the drug.
v. The fourth step of the process is the FDA drug review. First, a pharmaceutical company submits a New Drug Application, then FDA reviews the drug and approves or rejects it. Finally, an FDA advisory committee provides their input.
vi. The last step in the drug development process is FDA post-market drug safety monitoring. This is where FDA reviews reports of problems with drugs and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues.

To perform any clinical trial a protocol is set to ensure that the trials will meet the standards of Good Clinical Practices, hence a protocol can also be called the ground foundation of clinical studies. A clinical research project's background, justification, goals, design, technique, statistical considerations, and structure will all be covered in the study protocol.

The purpose of safeguarding the rights, safety, and well–being of all human research participants during clinical trials is done by the institutional review board (IRB). Also to approve a research protocol, the IRB must ensure that:

- Participants' risks are tolerable in light of the expected benefits.
- There is fairness in the selection of participants.
- Sufficient measures are taken to oversee the gathered data in order to guarantee the security of the individuals involved.
- Sufficient measures are implemented to safeguard participants and uphold data confidentiality.
- Extra protections are incorporated for susceptible groups. Obtaining and recording informed consent is done correctly.
- Emergency use(life-threatening and severely debilitating situations) of test articles.

In cases of emergency, the test articles may not require IND and FDA may authorize the shipment of the test article in advance of the IND submission.

One such situation emerged during the pandemic of 2020 that led to the emergency use of unapproved investigational drugs or new approaches of approved drugs such as Hydroxychloroquine sulfate and Chloroquine phosphate, Remdesivir to name a few.

In addition to these vaccines were also going through vigorous testing globally. Some vaccines that passed the first three phases of clinical trials were administered to the people namely Covaxin, Covishield in India. The last phase of clinical trials i.e post marketing surveillance is still ongoing and researchers are observing the long term effects of the vaccine.

As per the goverment sites more than 48 crore citizens have been vaccinated in India and the all the citizens are supposed to be vaccinated by the end of December.

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