RBDCOV Project

Specialised Articles - VERISTAT
#2 How Vaccine Clinical Trials Work?

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How Vaccine Clinical Trials Work?

Since August 2021, the Veristat team, in collaboration with our HIPRA colleagues, has been leading data management, clinical database programming, biostatistics and SAS programming, project management, clinical monitoring, medical monitoring, and consulting to facilitate overall RBDCOV consortium members' synergy and alignment of HIPRA's COVID-19 vaccine development programmes. RBDCOV is one of 11 high-profile projects selected by the European Commission as part of the Horizon Europe Programme, the largest programme for funding emergency research and innovation to prevent, mitigate, and respond to the impact of coronavirus and its variants. Our team has been working on several clinical studies, from phase II to phase III, covering first, healthy volunteers, and as part of the RBDCOV project, volunteers living with immunocompromising conditions, now moving on to adolescents.

HIPRA received marketing authorisation from the EMA for BIMERVAX® on 30 March 2023, less than two years after the start of the phase II trial. This is the first bivalent recombinant protein COVID-19 vaccine to be authorised in the EU and the first human health vaccine to be designed and developed in Spain.

Additionally, on 01 August 2023, BIMERVAX® was authorised by the Medicines and Healthcare Products Regulatory Agency (MHRA). It became the ninth COVID-19 vaccine to be authorised by the UK's independent medicines regulator.

Vaccines have a long history of successfully protecting people and communities against infectious diseases. Vaccination has improved the quality of life for many, and serious diseases like smallpox have been eliminated. As vaccine technologies advance, researchers can develop better and safer vaccines.

The Clinical Development of a Vaccine

The clinical development of a vaccine spans a three-phase process, which may include a fourth phase if the vaccine is approved by medicine regulators.

Phase I

Small groups of people (20 to 100) receive the trial vaccine. During this phase, researchers gather information on how safe the vaccine is in people. This includes learning about and identifying major side effects, and studying if the vaccine can cause an immune response.

Phase II

The clinical trial expands to hundreds (100-300) of trial participants who have characteristics (such as age and physical health) similar to the intended recipients of the vaccine. They should

also include groups of people from diverse backgrounds to ensure representation across different populations.
A Phase IIb trial, in particular, provides additional safety information on side effects and risks and is pivotal in assessing how well the vaccine works to cause an immune response.
Phase III
The clinical trial expands to thousands (1,000–3,000) of selected people. In this phase, researchers confirm how well the vaccine works, intensively monitor side effects, including less common adverse events (or unfavorable medical occurrence) , and collect all necessary information to support its safe use in people on a larger scale.
Phase IV (After approval)
After a vaccine is approved for use in the general population by medicine regulators, it may advance to an additional clinical trial phase with thousands of participants. Phase IV is a formal, ongoing study to evaluate the new vaccine's safety and effectiveness over a longer period. More safety data is collected as this phase involves the entire population, which is more diverse.
Phase IV trials provide ongoing information on:

- Vaccine safety
- The immune response to the vaccine
- Vaccine efficacy (how well the vaccine prevents the disease)

Since clinical trials are experiments in humans, they must be conducted following established standards to protect the rights, safety, and well-being of the participants. These standards include the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines and standards strictly regulated by each country. Safety evaluation is a central component in all stages of the drug development lifecycle. Before the marketing authorisation of a drug, rigorous safety monitoring and evaluations from preclinical to all stages of clinical trials are required. Detecting information on adverse events early on leads to better protection for the participants and as such, ongoing monitoring of safety parameters is required. Additionally, the quality of the data generated is pivotal to ensure the results can be trusted.

Clinical Development of BIMERVAX®

RBDCOV'sPhase IIb and III studies have shown that BIMERVAX®, HIPRA's vaccine, is safe and less reactogenic (capable of causing a reaction) with a broad ability to neutralise major SARS-CoV-2 variants, including Omicron variants. The comparative study versus the mRNA vaccine required by the EMA shows that, at six months after receiving the booster dose, people vaccinated with the BIMERVAX® vaccine have higher levels of virus-neutralising antibodies against all variants studied, suggesting more lasting protection. The RBDCOV Project trials aim to demonstrate these protective effects on children, adolescents, and people living with immunocompromising conditions.
BIMERVAX® contains part of the SARS-CoV-2 spike protein from the alpha and beta virus variants, which have been combined into a single protein. The vaccine also contains an adjuvant (a substance or group of substances) designed to help strengthen the immune responses to the vaccine and is based on a widely-used technology known in the manufacture of vaccines, such as hepatitis and influenza, among others.
The vaccine is stored at a refrigerated temperature between 2 and 8ºC, facilitating storage and distribution. This is a "ready-to-use" vaccine, i.e., it does not need to be reconstituted before use, thus making it easier for healthcare personnel to administrate.

Collaboration Highlights

Timelines for setting up and performing activities associated with the different clinical milestones were extremely tight to accommodate expectations and submission timelines to regulatory authorities. As such, the Veristat team needed to be flexible and adapt accordingly.
In the spirit of continued collaboration between HIPRA and Veristat and all the other partners that are part of the RBDCOV Consortium, as well as the mutual drive for efficiency throughout a clinical trial, below are some process insights on how the HIPRA and RBDCOV programmes have been conducted.

1. **Scheduling of a kick-off meeting across project trials:** A project kick-off meeting brings all team members involved together from across the various studies. This meeting ensures that everyone has a shared understanding of the goals, required deliverables, and workflow. The kick-off call discussion brings forward the identical responsibilities and tasks for each member of the team to support uniformity and consistency across trials. Conducting one centralised meeting also supports efficiencies in processes and team training.

2. **Drafting protocol and all essential documents for review early on to get a head start and design, setup, and test the clinical trial management system before the trial starts:** This was very important for this project given the tight timelines to respond to the global emergency. For context, the average time for database building until the launch of the RBDCOV trials was 3 weeks, whereas a typical database building time is 12 weeks. In addition, a Community Advisory Panel led by the EATG, the RBDCOV partner in charge of community engagement, reviewed the protocols and trial materials for participants to ensure they were accessible, complete and transparent, while reflecting participants' needs and preferences.

3. **Coordinating protocol updates, final protocol, and database live:** The whole team should work together to update the database on an ongoing basis based on protocol updates. With the RBDCOV trials, once the final version was ready and testing complete, the database went live shortly after.

4. **Establishing a global, versatile, and responsive team of clinical trial experts:** An extended team spread over different time zones enabled the expedited delivery of documents. A strong and experienced workforce was required to absorb the periods of high work demand. As an example, HIPRA topline interim results for the phase IIb study were delivered after 28 consecutive hours involving more than 40 professionals across 3 continents.

5. **Coordinating data cleaning:** All data should be cleaned and reconciled during the entire course of the trial and encompass database data, external data coming from vendors, laboratory data, and Serious Adverse Event (SAE) reconciliation. All the data gathered was reviewed and cleaned on an ongoing basis to ensure all adverse events, laboratory results, and other parameters were as expected. This was done to ensure the safety and well-being of the participants and provide meaningful data so that there was enough information for the authorities to decide on the approval.

6. **Securing the database lock:** The database should be locked once all of the data is cleaned and ready for analysis. Biostatisticians will then gather this information and provide a statistical analysis of the efficacy and safety of the vaccine.
7. **Submitting final study report:** Once the trial is complete and all data has been analysed, a final report is submitted to the authorities, where 100% of the analysed data is included.

Addressing the Ongoing Challenges of SARS-CoV-2

Continuing to face the challenges surrounding COVID-19 has required an ongoing and concerted effort by several committed resources in conducting these clinical studies. One such resource for which HIPRA leads its consortium is the previously mentioned RBDCOV Project, the umbrella Project under which two of HIPRA's studies fall. The Project's mission is to protect people not only from severe COVID-19 disease, but also prevent or reduce infection in all vaccinated populations including individuals living with immunocompromising conditions and children and adolescents.

Challenging projects with tight timelines and fast-moving working environments have been common in the RBDCOV Project which has required exceptional teamwork across internal teams and excellent communication so that each of us can deliver on demand. Veristat is proud to work with HIPRA and the RBDCOV Project partners and their dynamic and experienced teams, as we work together to solve complex challenges.

Veristat's expertise comes from planning or conducting more than 70 COVID-19 projects for a broad range of therapies, including anti-inflammatories, antivirals, antiseptics sprays, cannabinoids, advanced therapies, probiotics, monoclonal antibodies, and vaccines.
To learn more about Veristat, please visit www.veristat.com