Phase I (first-in-man) prophylactic vaccine’s clinical trials: Selecting a clinical trial site

An appropriately equipped and staffed Phase I unit is critical for smooth conduct of a first-in-man clinical trial. The first-in-man prophylactic vaccine trial(s) requires basic infrastructure of clinical trial site, experienced and dedicated site staff and healthy adults as volunteers. The facility should have access to equipment, emergency services, laboratory, pharmacy and archiving. In terms of design, infrastructure, workflow and manpower, a Phase I unit for testing a novel vaccine or drug are quite similar. However, there are some important attributes, which should be taken into consideration, while performing pre-trial site selection for conducting phase I trial with a new or novel vaccine.

Key words: Clinical trial site, infrastructure, manpower, Phase I unit, subjects, vaccine

INTRODUCTION

For planning and conducting vaccine clinical trials in India, the Central Drug Standard Control Organization (CDSCO) guidance document “Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India, 2012”[1] and Schedule-Y[2] can be referred to. In addition, relevant guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[3,4] World Health Organization,[5-7] European Medical Agency[8-10] and United States Food and Drug Administration[11-13] can be consulted. However, a separate detailed guideline on preclinical and clinical development of vaccines from the Indian National Regulatory Authorities (NRA) is awaited and is part of recent recommendations given to CDSCO by an Expert Committee.[14]

In India, there is a growing need for developing capacity to conduct Phase I studies as both new and novel vaccine candidates need to undergo Phase I clinical trials. This narrative is an attempt to highlight some of the key points to consider, while selecting a clinical trial site for conducting a Phase I, first-in-man prophylactic vaccine clinical trial. Vaccines may be of different types like live attenuated, inactivated, sub-unit, toxoid, polysaccharide, conjugated or DNA vaccines. The different type of vaccines can impact the study design, investigations and follow-up, but the general principles of selecting a Phase I site stay the same. These trials can either be conducted in the setting of Clinical Pharmacology Units (CPUs) dedicated to clinical pharmacology studies in healthy adult volunteers or in hospital based units with access to healthy adult population and a system to track the volunteers.
In addition, Phase I vaccine clinical trials may also allow testing the preliminary efficacy of vaccine candidate in a “challenge model.” These are also called Phase I/IIa studies. In such a study, healthy immunized volunteers are intentionally exposed to the infectious disease, which the vaccine is intended to prevent.¹⁵,¹⁶ Such studies are also encouraged to be done in a controlled environment of a CPU where participants receive round-the-clock medical attention during the days they develop the disease.

**PHASE I UNIT: VACCINES VERSUS DRUGS**

Though same clinical trial facilities can be used for Phase I clinical trials of vaccines and drugs, but the attributes pertaining to the study conduct with vaccines allow more sites to be considered as potential vaccine clinical trial units. The predominant differences between studies with vaccines and drugs, while conducting a Phase I clinical trial are:

1. Vaccine Phase I trials are comparatively long-term (~6-12 months) vis-à-vis 1-3 months Phase I trials of a drug. Hence, a strong subject tracking capability is required at the clinical trial site.
2. Repeated blood samples for studying 24-h pharmacokinetics is not required for vaccines.
3. Volunteers rarely need to stay overnight at the clinical trial facility during a vaccine trial. Hence, facilities for volunteer admission in the unit are not a prerequisite.
4. There is a general fear that risk of “hypersensitivity” as an adverse reaction can be higher with a vaccine product since majority of products are administered through parenteral route. Therefore, extra caution is advised when it is administered for the first time in humans.
5. Novel vaccine candidates very often require extemporaneous formulation preparation of the vaccine before immunization. Hence, a strong support of a well-trained pharmacist is required along with specific infrastructure, e.g. laminar flow hood for aseptic preparation of vaccine formulation.
6. Depending upon the storage directions, the vaccine may need to be stored at -70°C/ -20°C/2-8°C; hence, appropriate provisions in the pharmacy for deep freezers and refrigerators is needed.

To address the aforementioned issues and other points of special interest, the clinical trial site selection for a Phase I vaccine trial has been discussed under the headings of infrastructure, trained manpower and research subjects.

**Infrastructure**

**Phase I unit**

For purpose of ease, the selection criteria have been divided into critical and noncritical parameters. However, these divisions should be considered as mere guidance and can change as per the need of study protocol:

Critical (mandatory) parameters if overnight stay not required:
- Subject screening/counseling areas to administer and record Informed Consent.
- Physical examination room(s) with qualified equipment for performing various tasks (e.g. sphygmomanometer, measuring tape, weighing scale etc.)
- Secure computer systems that have access rights.
- Space for withdrawing blood samples (phlebotomy stations/chairs).
- Pharmacy/investigational medicinal product (IMP) storage area with proper handling processes well laid out in standard operating procedures (SOPs). There should be provision for refrigerators and deep-freezers with temperature specifications and back-up options in case of failure.
- Emergency facilities comprising of a bed, crash carts, emergency medicines and clear instructions for carrying out emergency procedures. The crash cart should be equipped with cardioverter-defibrillator, equipment to secure airway and restore breathing (such as laryngoscope, endotracheal tubes, AMBU mask and bag, self-inflating resuscitator etc.), oxygen supply, suction tube, emergency medicines to rescue patient from anaphylaxis or circulatory collapse (such as injection adrenaline/epinephrine, intravenous fluids, sodium bicarbonate solution, high potency steroids, anti-histaminic, amiodarone, calcium gluconate). Availability of a simple to operate medical ventilator machine can be lifesaving in case of need and is an added bonus for the facility to have until patient can be transferred to an Intensive Care Unit (ICU).
- Fire proof cabinets for document storage in a dedicated area.
- Catering service for providing meals to subjects during the observation period after immunization.
- Access to Good Clinical Laboratory Practice compliant laboratory with accreditation from at least national agency like National Accreditation Board for Testing and Calibration Laboratories (NABL).
- Imaging facilities (X-ray, ultrasound etc.): If not available within the unit then must be accessible through an associated hospital(s) or a nearby diagnostic center.
- All the activities in the unit must be timed. All time must be noted from the electronic GPS synchronized wall clocks. It is desirable that the computer systems clock and equipment clocks are also synchronized.
- Equipment (video camera of appropriate resolution,
A Phase I unit should either have an in-house or easy access to an accredited clinical laboratory. The study protocol or sponsor can guide the need for accreditation from NABL or CAP. In addition, the facility design of clinical laboratories must be according the “biosafety hazard level” for testing of human blood samples and the infrastructure should ensure adequate separation of different activities in the laboratory beginning from sample receipt and storage to the final analysis, documentation and reporting of results. Through this workflow, the tasks must be managed by staff trained on Good Clinical Practice (GCP). It is essential that subject’s confidentiality is not compromised.

Laboratory for assessing immunogenicity

The laboratory testing of the immune response in human sera forms an integral part of Phase I vaccine clinical trials. The immune response is tested either in the sponsor’s laboratory or the activity is outsourced to an external laboratory. In both cases, the following needs to be ensured:

• The assay (ELISA, neutralization assays, opsonophagocytic assays etc.) utilized to test the immune response are at least partially validated on parameters such as accuracy, specificity, precision, linearity, and lower limit of detection. The method development report should be reviewed.

• Written SOPs encompassing all activities involved, study specific laboratory manuals and work instructions are available.

• The equipment/instruments and the computer systems, which process, analyze, store and report the data must be validated.

• The entire process must ensure maintenance of an audit trail.

• Site should have the capability to send sera samples maintaining a cold chain. The person responsible for shipment should receive training from the courier.
agency on “dangerous goods management” and “cold chain management” provided by International Air Transport Association.

Ethics committee
- Schedule Y or ICH E6 does not give any special recommendation for the Constitution of an Ethics Committee, while evaluating a Phase I vaccine clinical trial protocol
- As mandated by Schedule-Y/Indian Council of Medical Research guidelines the IEC chairman shall be independent of the institution and on matters related to the study only members independent of the clinical trial and sponsor will have the voting rights. The IEC will be registered with the office of CDSCO and shall keep itself abreast of changes in the regulatory requirements.

Manpower
Evaluation of the unit must involve assessment of the qualifications, experience, willingness and ability of the investigator(s) and the site staff with regards to their participation in a Phase I vaccine clinical trial.

Investigator(s)
In a Phase I unit, the clinicians constitute the most important part of the study team. While constituting a team, they are usually designated principal investigator (PI)-the team leader, sub-investigator and study doctor.

Principal investigator has the final responsibility for safety and well-being of the trial subjects therefore it’s preferable that the PI be a postgraduate in the field of medicine. Background knowledge of early clinical development of vaccines and experience of supervising a Phase I trial is an added advantage. While choosing the study team it is prudent to evaluate the capability of the team on AE assessment, reporting and management specifically during a vaccine clinical trial. Training of the clinicians on AE assessment on Adverse Events Following Immunization (AEFI)[3,17] would allow objective assessment of solicited AEs. In developing countries where the CPUs have little experience of conducting early phase studies, it is advisable to at least have one practicing clinician in the study team. This is desirable since evaluation of AEs and other safety related issues will require experience and sound clinical judgment. A clinician also plays an important role during trials with live or killed vaccines as there is potential of clinically significant infections in the recipients or in contacts through reversion to virulence and shedding of micro-organism. A clinician who may not have received training on GCP, but displays good knowledge of his/her subject is also a suitable candidate to lead the team, provided the necessary trainings are imparted prior to trial initiation.

All members of the team must be trained in GCP and must take up the responsibility for maintaining documentation.

A Phase I vaccine trial usually demands in-house observation for few hours of the trial subjects during the day of vaccination and repeated follow-ups for next few days. Therefore, round the clock presence of entire study team is generally not required.

Support staff
The screening physician should be able to screen healthy volunteers and seek relevant past history, which could impact the immune response to the vaccine candidate. The enrolment team should also be involved while tracking the subjects for follow-up visits.

All the nurses must be qualified and GCP trained. They should have had training in managing medical emergencies, basic life support and recording vitals. On the day of vaccination, it would be ideal to have a nurse available in the unit who has experience of working in the ICUs.

Adequately trained project coordinators and project managers are critical for appropriate documentation.

Research subjects
Though there have been discussions on the ethics of recruiting healthy subjects in Phase I vaccine studies, knowing that the trial participants will not be directly benefited from the vaccine candidate, but they still remain the ideal choice when it comes to testing a novel vaccine for the first time in humans even if the vaccine is for use only in children. The inclusion/exclusion criteria for subject selection with regards to their physical and mental health along with a healthy social background remain standard for any first-in-man study with a drug/pharmaceutical. However, since vaccines differ in terms of specific safety issues and also their mode of action, following issues may be considered while recruiting subjects:

- Ideally, the subjects are recruited from an area not endemic to the disease and a baseline antibody titer be studied so as to avoid queries on sero-conversion and fold response
- During clinical development of vaccines not specifically intended for use during pregnancy, pregnant women are ineligible to participate in clinical trials. Recruitment of women of child bearing potential in a Phase I study is a critical decision, which should be debated with the approving NRA. When women of child bearing age participate, the unit has to take all measures to eliminate the chance of in utero or lactation exposure by proper screening and informed consent procedures. The female participants need to strictly follow birth control measures as delineated in the protocol
Phase I vaccine studies usually have a long follow-up of 6 months to 1 year. To ensure complete follow-up, recruitment of migrant populations must be avoided.

The AEFIs are generally recorded for 5-7 days postvaccination, however, with greater possibility of delayed adverse reactions with live or killed vaccines the subjects and Investigators must record more detailed information for a longer duration (minimum 14 days).

Vaccines work by generating the immune response in human body. Therefore, prospective subjects should be screened for chronic intake of immunosuppressants like steroids or other immune modifying drugs, any recent vaccinations or treatment with immunoglobulins, all of which could impact/modify the immune response against the vaccine which is being studied.

CONCLUSION

Phase I vaccine studies are executed on similar principles as later phases of clinical development. However, the major difference between different phases of novel vaccine development is in “the objective,” “end point” and “target population.” While Phase I vaccine clinical trial of a novel vaccine always measures the immune response the Phase II/III trials study the efficacy in addition to measuring the immune response against the vaccine candidate.

Phase I vaccine trials typically are dose escalation studies where the higher doses are tested after evaluation of safety data of the previous dose.

Unlike for bioavailability-bioequivalence (BA-BE) studies, no separate guidelines are available from CDSCO on requirements of a Phase I clinical trial site. It is left to the best judgment of the sponsor to choose an appropriate site based on the requirements of study protocol, study risk assessment and their SOPs. Since India has presence of many BA-BE centers these sites could be considered as possible Phase I sites only if they demonstrate vicinity to or location within a tertiary care hospital with immediate access to their ICU, specially equipped and designed Phase I clinical unit, clinicians as PIs, project team trained on handling unknown AEs and have demonstrated in past ability to handle such trials.

The features mentioned above for a Phase I vaccine clinical trial site should not be considered as an exhaustive list. The recommendation is to evaluate the specific requirements of the study protocol, in-house SOPs and supplement it with the aforementioned attributes before making the site selection visit.

ACKNOWLEDGMENT

MVDP acknowledges the support provided by Bill and Melinda Gates Foundation in supporting the program.

REFERENCES

1. DBT, Ministry of Science and Technology and CDSCO, Ministry of Health and Family Welfare, Government of India: Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India; 2012.
2. CDSCO, Ministry of Health, Government of India: Schedule Y (Amended Version 2005) Under Drugs and Cosmetic Rules; 1945.
3. ICH S6 (R1) Guideline: Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals; June 1997 (Addendum dated June 2011).
4. ICH M3 (R2) Guideline: Guidance on Nonclinical Safety Studies for the conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; June 2009.
5. WHO Guidelines on Nonclinical Evaluation of Vaccines. WHO Expert Committee on Biological Standardization. Fifty-Fourth Report. Annex 1. Geneva: World Health Organization; 2005. (WHO Technical Report Series, No. 927).
6. Guidelines on Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines. Geneva: World Health Organization; 2013.
7. Guidelines on Clinical Evaluation of Vaccines. WHO Expert Committee on Biological Standardization. Fifty-Second Report. Annex 1. Geneva: World Health Organization; 2004. (WHO Technical Report Series, No. 924).
8. Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines. London: European Medicine Agency; 1997.
9. CHMP/STR/465/95.
10. Guideline on Clinical Evaluation of New Vaccines. London: European Medicine Agency; 2006. EMEA/CHMP/VEP/164653/2005.
11. Guideline on Adjuvants in Vaccines for Human Use. London: The European Medicine Agency; 2005. EMEA/CHMP/VEG/134716/2004.
12. Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases. Centre for Biologics Evaluation and Research, United States Food and Drug Administration; 2011.
13. Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications. Centre for Biologics Evaluation and Research, United States Food and Drug Administration; 2006.
14. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Centre for Biologics Evaluation and Research, United States Food and Drug Administration; 2007.
15. Report of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for approval of New Drugs, Clinical Trials and Banning of Drugs; 2013.
16. WHO Guidelines on Quality, Safety and Efficacy of Recombinant Malaria Vaccines Targeting the Pre-erythrocytic and Blood Stages of Plasmodium falciparum, Technical Report Series, 980, Annex 3, 2012.
17. Brighton collaboration. Available from: http://www.brightoncollaboration.org/public. [Last accessed on 2014 Nov 05]