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Perspective

Early phase clinical trials in India: Need & scope

The COVID-19 pandemic has strengthened, accelerated and changed many aspects of vaccine, drugs, device development and clinical research. There has been a global response. Indian regulators, industry and society responded rapidly. Countries such as the UK were ready with nuts and bolts of clinical trials. However, in general, low middle-income countries (LMICs) lagged behind and were not sufficiently represented in major clinical trials and did not have enough local data or evidence to inform country-specific policy.

Responses to COVID-19 – India's success story

India succeeded in getting indigenous vaccines developed and approved and COVID-19 testing facilities ready. Regulatory changes were announced to help tide over the COVID-19 related constraints, and at the same time to allow COVID-19 vaccines to be made quickly available through emergency use authorization. In addition to exporting face masks, personal protective equipment (PPE) kits, and diagnostics to both developed and developing countries, India also provided vaccines to its neighbouring countries and abroad.

Gaps in clinical research in India

Among the trials registered in Clinical Trials Registry-India, while a large number was related to COVID-19, non-COVID trials were also registered. However, as there were gaps in implementation, some of the clinical trials particularly those required for policy decisions, could not be completed equally and rapidly.

Bassi *et al*[1] published the challenges in operationalizing clinical trials in India. While it highlights issues pertaining to the COVID-19 pandemic, many of these were systemic in nature and important from non-pandemic related clinical trial perspective as well. There were important site level challenges namely lack of site set up, previous experience with trial conduct and use of digital platform, lack of participation by remote and smaller health units, and delays between submissions to ethics committees and receiving their approvals.

Need & opportunity to strengthen early phase clinical trials in India

India has well developed facilities for manufacturing of generic (off-patent) small molecule drugs and vaccines which are exported to both developed and developing countries. India also conducts bio-availability and bridging studies for small molecule drugs (in place for the last 25 yr) before introducing them in the country to examine if they are well tolerated and safe in our multicultural society with genetic variations. In case of biosimilars which have a use duration of more than five years in countries with well regulated market approvals (*i.e*. FDA and EUA, Australia and Japan regulated) and post-marketing data for five years is available, only bridging studies are needed before getting marketing permission for them in India since 2012.

In the past, majority of the new drugs came from the USA and Europe. However, in the last few years, Indian Pharmaceutical Industry has moved towards manufacturing complex generics including biosimilars and also focusing on producing key active pharmaceutical ingredient (APIs). Importantly, the biotech sector has focused on vaccines and recombination therapeutics and is moving towards new product development.

Government organizations such as Central Drug Research Institute (CDRI), Indian Institute of Integrative Medicine (IIIM) and other Council of Scientific & Industrial Research (CSIR) organizations are now actively pursuing new drug development. The development of phytopharmaceuticals has been initiated under various schemes and there are about

15 of them in the pipeline. International organizations such as drugs for neglected diseases Initiative (DNDi), are developing drugs for tropical diseases and are turning to India for early phase clinical trials.

Moreover, there has been an upsurge in clinical trials for Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy (*AYUSH*) products. An analysis of *AYUSH* studies registered in the Clinical Trial Registry of India during 2009 to 2020 showed that out of total 27,075 trials registered, 3532 were *AYUSH* studies. Ten per cent of them involved healthy volunteers, 6.53 per cent were phase I, 32.75 per cent were phase II, 10.32 per cent were phase III studies (for half of the studies a mention about the phase of the study was not available). Most of the studies[2] (75%) were being supported with Government Medical College funding. The industry contributed very little[2].

The opportunity for trial in India was available for both Indian as well as global products. Worth noting is that there exists a globally expressed need for multi-regional clinical trials (MRCT). In 2014, International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH) E17 MRCT guideline[3] was drafted by ICH working group and trial guidance was accepted in 2017. The overarching goal was to encourage simultaneous global development and near-simultaneous registration of innovative medicines. The aim was to accelerate the drug development process and shorten the approval time. With the socialistic public health objective of access and equitable distribution, MRCTs are important to address unmet needs. For global development, it is important to consider country-specific effect modifiers of drug/vaccine efficacy, effectiveness, adverse drug reactions (ADRs), which could be due to intrinsic factors such as genetics and diseases prevalence and/or extrinsic factors such as culture, socioeconomic issues and food habits. Knowledge of these factors, a right attitude of industry, investigators and regulators to design studies, trained workforce, capacity to plan, carry out and interpret such studies are important. In the absence of considerations around effect modifiers, regulatory agencies would be reluctant to accept the data from other countries and would demand local clinical trials, resulting in delay in the final registration and access to local population[4].

The questions that follow are - when is the best time to include a country in Monte Carlo ray-tracing? Is a local phase I trial needed? The earlier the investigation into effect modifier is planned, the more likely it is for the global data to get accepted for registration.

The global clinical trial market size was estimated to be US $ 44.3 billion in 2020. In 2020, phase III formed 53.2 per cent, phase II, 19.6 per cent and phase I, 15 per cent of the total cost. By 2028, phase I and II trials are expected to increase further. North America has dominated with the largest revenue share of 51 per cent in 2020. However, Asian-Pacific market is expected to grow faster with compound annual growth rate (CAGR) of 6.7 per cent.

As per IMS Health, Quintiles, VIA (IQVIA) statistics (2021)[5], globally funding for early and late stage research & development (R & D) increased significantly in 2020. The number of first time launches of novel active substance reached an all time high in 2020. Clinical trials increased eight per cent in 2020. Emerging biopharma companies originated and launched 40 per cent of all new drugs in 2020[6]. These statistics emphasize growing demand for early phase clinical trials. However, there is an under representation of African-Asian ethnic groups in clinical trials conducted in the USA.

There is an advantage to India. The clinical study cost structure is estimated as 30-35 per cent for skilled workforce, 20-25 per cent for clinical data management, 20-25 per cent for clinical monitoring, 10-15 per cent for site recruitment, 10-15 per cent for other staff recruitment, 12 per cent for patient recruitment and five per cent for clinical procedure and laboratory costs. It is estimated that regional players' cost of operations is 20-40 per cent less than global ones, as they have lower overheads, and are structurally less complex due to local decision-making. During the COVID-19 pandemic, emerged a demand to conduct global trials in Asia[7].

Benefits of doing early phase clinical trials in India

Early phase clinical trials provide experience with the new drugs, evaluating behaviour of the drug in humans, gather preliminary data on safety, pharmacokinetics, pharmacodynamics, select promising lead candidates and help deciding upon appropriate doses. This supports further development with the assessment of dose, indication, risk-benefit specification for the Indian population considering intrinsic such as pharmacogenetics and extrinsic factors such as food-health system affecting drug response.

This in turn allows early access to medicine at lower cost, especially for unmet needs in India, related to infectious diseases like malaria, tuberculosis (TB), drug resistant Kala azar, and rare diseases.

Challenges

However, there are challenges and concerns about potential exploitation of the Indian population. The regulations for clinical trials as stated in the Drugs and Cosmetics Act are therefore cautious and do not allow drugs developed elsewhere to be tested first in human beings in India. This has deterred testing of compounds in early-stage phase clinical trials, although there is a clause of exception for the country's need. There is also concern about the availability of centres with suitable infrastructure facilities, experienced trained workforce, access to participants, lag time to get regulatory and ethics committee approvals.

A recent Council for International Organizations of Medical Sciences (CIOMS) report summarized the obstacles and enablers for clinical research in LMIC like India, which include creating a research friendly environment and building infrastructure and capacity[8]. Presently, there are very few centres with experience in phase I studies. Of approximately 22 global and eight regular Contract Research Organizations (CROs) and Indian Council of Medical Research (ICMR) product development centres, only a handful can carry out phase I studies.

Way forward

There is a need to strengthen the capacity to carry out clinical trials and clinical research. India has a vast network of healthcare facilities, with approximately 30,000 primary healthcare centres, 150,000 sub-centres, 69,000 hospitals of which 43000 are private. It has 595 medical colleges, with 89395 student intake capacity, 1.2 million registered doctors, of whom 0.37 million are specialists (actual numbers in practice may be less). There are also approximately 0.5 million ayurvedic doctors.

The ICMR has a long history of conducting and supporting clinical research through its task force, centres for advanced research, *ad hoc* projects and fellowships. It has registries such as for stroke, which are useful for conducting clinical trials. It has also set up clinical studies and trial Unit (CSTU). Furthermore, ICMR-Institutes on TB, Kala-azar, diarrhoeal diseases, immunohaematology, malaria and reproductive health have established mechanisms for conducting clinical trials. In 2019, ICMR set up product development centres and rational use centres under the National Virtual Centre for Clinical Pharmacology with a capacity to carry out phase I – IV studies, which have carried out studies on COVID drugs[9]. There is now a need to increase the number of these centres, especially for early phase clinical trials. Noticeably, the process for establishing four clinical phase I trial facilities of international standards in the country has already been initiated by the ICMR. The scope of such centres could involve stand alone facilities and units in the hospital or, academic settings (*i.e*. a commercial organization or a non-commercial clinical research facility) to carry out phase I and early phase trials in healthy volunteers, patient volunteers and could include phase 0 or, micro-dosing.

Government of India has recently announced that its facilities will be open to private industry, pharmaceutical industry, and start-ups. Noticeably, in National Institute of Pharmaceutical Education and Research (NIPER), Pharmacy Colleges, Institute of Chemical Technology (ICTs), Indian Institute of Technology (IITs), drug development is already being sponsored by industries. What appears important at this juncture is attaining a financial sustainability and ensuring a connect between health science universities and academic public and private health institutions and hospitals. This could be achieved by joint academic programmes and the phase I centres committing/ contributing to service, training and research for drug development.

Although the COVID-19 pandemic has accelerated basic research as well as clinical drug development globally, LMICs have lagged behind. India, during this pandemic, contributed enormously to vaccine development as well as exporting locally made masks and PPE kits. However, there is a need to strengthen its capacity to carry out early phase clinical trials in order to promote access and equitable distribution of quality assured safe and effective health products for unmet needs. India is strategically located to contribute immensely to MRCT and to the global development, besides serving its own people.

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