Original Article

A review of clinical trials registered in India from 2008 to 2022 to describe the first-in-human trials

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Abstract

Aim: This analysis was conducted to review the number, and describe the characteristics of first-in-human (FIH) Phase 1 clinical trials registered in India from 2008 to 2022.

Materials and Methods: The data were extracted from the Clinical Trials Registry – India database for all FIH Phase 1 clinical trials registered between 2008 and 2022. Early-phase trials that were not FIH trials (e.g., pharmacokinetic studies and drug–drug interaction studies) were excluded from the study.

Results: A total of 1891 trials were retrieved and 220 were included in the analysis. Most of the investigational products were drugs (55%) followed by vaccines (38.2%). The most common therapeutic class of drugs was cancer chemotherapy (19.8%), followed by antimicrobial chemotherapy and endocrinology (18.2% each). The most common vaccine was the influenza vaccine (21.4%), followed by the measles–mumps–rubella vaccine (15.5%). The pharmaceutical industry was the predominant sponsor for most (91%) of the Phase 1 trials. Of the top five sites where most of the Phase 1 trials were conducted, three were private nonacademic centers (cumulatively 31%) and two were tertiary care medical colleges (cumulatively 9%).

Conclusion: Phase 1 clinical trials seem to be conducted in India predominantly with industry sponsorship. There is a need to have an alternate ecosystem to take forward molecules that do not receive adequate attention from the industry and molecules that are of national health priority other than areas such as chemotherapy, antimicrobials, and endocrinology. The Indian Council of Medical Research is setting up Phase 1 clinical trial capacity for molecules that predominantly may arise from nonindustry channels.

Keywords: Clinical Trials Registry – India, Indian Council of Medical Research, investigational new drugs, Phase 1 clinical trials

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INTRODUCTION

First-in-human (FIH) Phase 1 trials aim to evaluate the safety and tolerability of medicines or vaccines as investigational new drugs (INDs) in humans before they proceed to further clinical trials. Phase 1 trials usually involve the study of one or a combination of the following: safety and toleration profile, maximum tolerated dose, pharmacokinetics, pharmacodynamics, and the correlations between these parameters.[1-3] Approximately 70% of drugs from Phase 1 move to the next phase.[2] FIH Phase 1 trials carry certain inherent risks, and therefore, their conduct requires specialized multidiscipline, cross-functional collaborative expertise, and a comprehensive infrastructure comprising a well-equipped inpatient facility and advanced laboratory support.[4] They generally include healthy volunteers as participants, even though patients are enrolled in specific disease areas and conditions. Thus, FIH Phase 1 trials are mostly nontherapeutic, and there is the additional dilemma of exposing participants to an IND with an incompletely known human risk profile. Nevertheless, this method is traditionally considered the most suitable to explore the safety and dose range of an IND showing potential for benefit from preclinical studies.[5,6]

The Indian pharmaceutical industry accounts for one-fifth of global generic medicine exports and meets over half of the global demand for vaccines.[7,8] Many domestic pharmaceutical companies have made substantial investments in new drug development and have several new molecular entities moving through the preclinical pipeline and into early-phase clinical trials. In recent years, the Government of India has also extended significant efforts toward streamlining regulations to facilitate academia and pharmaceutical companies to conduct clinical trials in India. It is noteworthy that the Indian Council of Medical Research (ICMR) has launched the Indian Clinical Trial and Education Network (INTENT), a pan-India network of clinical trial sites, with the overarching goal of providing evidence-based, robust, and culturally sensitive solutions to priority health problems of the country through conduct of large multicenter clinical trials.[9] Similarly, ICMR is in the process of rolling out a program to support the development of world-class Phase 1 clinical trial units in academic centers in the country to function as public infrastructure for early-phase clinical development of medical products. These facilities will be capable of planning and executing Phase 1 clinical trials of INDs that are of national health priority.

Registration of clinical trials is considered an ethical, scientific, and moral imperative.[10,11] A centralized, voluntary clinical trials register, the Clinical Trials Registry – India (CTRI), was launched in the country in July 2007.[12-14] It is hosted by ICMR's National Institute of Medical Statistics. In June 2009, the Drugs Controller General of India made it mandatory for regulatory trials to be registered with the CTRI (office order F No. 12-01/09-DC-[Pt 32]). The stated mission of the CTRI is to ensure prospective registration of all clinical trials in India, i.e. before the recruitment of the first participant. Trials registered on the CTRI are included in the World Health Organization's (WHO) central repository of clinical trial information – the International Clinical Trials Registry Platform (ICTRP).[15] Similarly, ClinicalTrials.gov, hosted by the US National Institutes of Health's National Library of Medicine, is a database of privately and publicly funded clinical trials conducted around the world.[16] With this background, this review was conducted to determine the number and characteristics of all FIH Phase 1 clinical trials conducted in India in the past 15 years from 2008 to 2022.

MATERIALS AND METHODS

This was a review based on data provided by the voluntary registrants of Phase 1 clinical trials in the CTRI database.[12] Data were extracted from the CTRI database[12] for all FIH Phase 1 clinical trials registered between January 1, 2008, and December 31, 2022. Only trials involving allopathic medicines and vaccines were included in the study. Traditional medicines, products in dentistry, and nutraceuticals were excluded from the study. Early-phase trials that were not FIH trials (e.g., pharmacokinetic studies and drug–drug interaction studies) were also excluded from the study. In addition, we looked into the ICTRP database[15] and the ClinicalTrials.gov database[16] for FIH Phase 1 trials that were conducted in India during the study period but not registered in CTRI. We also looked into these two databases[15,16] for FIH Phase 1 clinical trials sponsored by any Indian pharmaceutical company (ones that are headquartered in India) but conducted outside India during the study period. Data was retrieved and entered into a spreadsheet for the following information: year-wise number of FIH Phase 1 clinical trials, types of the various INDs and their therapeutic classes, nature of sponsor (academia, industry, or nongovernmental organizations), and respective trial sites. Descriptive statistics was used.

RESULTS

A total of 1891 trials labeled as Phase 1 trials in CTRI from 2008 to 2022 were extracted after excluding duplicates, and finally, 220 were included in the analysis [Figure 1a].

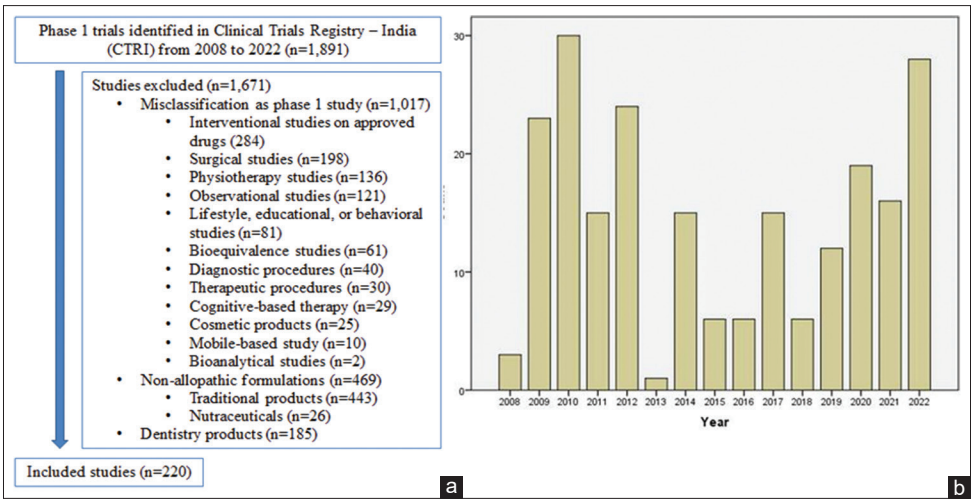

Figure 1: (a) The study selection process. (b) Year-wise distribution of the number of Indian first-in-human Phase 1 trials. CTRI = Clinical Trials Registry – India

Interestingly, 545 trials were found to have been misclassified in CTRI as Phase 1 clinical trials. There was no FIH Phase 1 clinical trial registered in ClinicalTrials.gov that was conducted in India but not registered in CTRI. However, from 2008 to 2022, there were over 75 early Phase 1 or Phase 1 trials registered on ClinicalTrials.gov that were conducted by major Indian pharmaceutical companies in the USA.

The year-wise distribution of the number of Indian FIH Phase 1 trials is illustrated in Figure 1b. There was a dip in the number of FIH Phase 1 trials in 2013, followed by a steady rise, particularly after 2018. The distribution of types of investigational products (drug, vaccine, cell, radiopharmaceutical, or device) is given in Table 1, together with the frequency of therapeutic class. Most of the investigational products were drugs (55%), followed by vaccines (38.2%). There were a few investigational stem cell products (5.8%), radiopharmaceuticals (0.5%), and medical devices (0.5%). The most common therapeutic class of drugs was cancer chemotherapy (19.8%), followed by antimicrobial chemotherapy and endocrinology (18.2% each). Among vaccines, the most common was the influenza vaccine (21.4%), followed by the measles–mumps–rubella vaccine (15.5%). The pharmaceutical industry was the predominant sponsor for most (91%) of the Phase 1 trials; the other sponsors were academic organizations (5%) and nongovernmental organizations (4%). Of the top five sites where most of the Phase 1 trials were conducted, three were private nonacademic centers from Western India (cumulatively 31%) and two were tertiary care medical colleges from the Southern (6%) and Northern (3%) regions of India, respectively.

Table 1: Distributions of the types of various investigational products that were evaluated in first-in-human clinical trials in India from 2008 to 2022 as extracted from the Clinical Trials Registry – India (*n*=220)

Type of investigational products	Number of FIH clinical trials (%)
Drugs	121 (55.0)
Cancer chemotherapy	24 (19.8)
Antimicrobial chemotherapy	22 (18.2)
Endocrinology	21 (18.2)
Central nervous system	12 (9.9)
Cardiology	12 (9.9)
Respiratory system	9 (7.4)
Hematology	7 (7.4)
Orthopedics and osteology	6 (4.9)
Gastroenterology	3 (2.5)
Ophthalmology	2 (1.6)
Dermatology	2 (1.6)
Autacoids	1 (0.8)
Vaccines	84 (38.2)
Influenza	18 (21.4)
Measles–mumps–rubella	13 (15.5)
Pneumococcal infection	7 (8.3)
Hepatitis virus	6 (7.0)
Diphtheria–tetanus–pertussis	5 (5.9)
Coronavirus disease	5 (5.9)
Typhoid	3 (3.6)
Tetanus	3 (3.6)
Rabies	3 (3.6)
Chikungunya	3 (3.6)
Human papillomavirus	3 (3.6)
Poliovirus	2 (2.4)
Rotavirus	2 (2.4)
Japanese encephalitis	2 (2.4)
Malaria	2 (2.4)
Chickenpox	2 (2.4)
Mycobacterium	1 (1.2)
Human immunodeficiency virus	1 (1.2)
Dengue	1 (1.2)
Zika virus	1 (1.2)
Yellow fever	1 (1.2)
Stem cell products	13 (5.8)
Radiopharmaceuticals	1 (0.5)
Medical devices	1 (0.5)

FIH = First-in-human

DISCUSSION

In this review, we found that a total of 220 FIH Phase 1 clinical trials were conducted in India between 2008 and 2022. The most common INDs were vaccines, cancer chemotherapy, and antimicrobial chemotherapy. Most of the trials were sponsored by the pharmaceutical industry. Interestingly, 545 trials were misclassified in the CTRI as Phase 1 clinical trials. Such misclassifications have been reported earlier, and some of the reasons for such misclassification have also been described.[14] Similar data quality concerns have been reported earlier by authors who reviewed the data from various clinical trial registries. A low consistency of key characteristics across seven trial registries (ClinicalTrials.gov, EudraCT, International Standard Randomised Controlled Trial Number registry, the German Clinical Trials Register, CTRI, the Australian New Zealand Clinical Trials Registry, and the Japan Primary Registries Network) was reported in a recent systematic review.[17] Inconsistency between key entries (e.g., primary outcome measures) in a trial registry (ClinicalTrials.gov) and published articles has also been reported.[18] The ICTRP also persistently lacks crucial information (contact details, interventions, and primary outcomes).[19,20] ClinicalTrials.gov was also observed to have deficiencies in important information.[21] There has been, however, a steady improvement in the quality of data in clinical trial registries after the release of the WHO Trial Registration Data Set, WHO International Standards for Clinical Trial Registries, and the International Committee of Medical Journal Editors' position statement on data quality.[18,22,23] Prospective clinical trial registration is associated with low risks of selection bias, performance bias, and detection bias as compared to retrospective clinical trial registration.[24] However, improper registration continues to remain a problem across the world, particularly for academic clinical trials that are government or nonindustry funded.[25]

There are several complexities in the conduct of clinical trials in India. In the past decade, clinical trials have been the subject of intense scrutiny. Trials are often portrayed as commercial activity by the media instead of a scientific endeavor to answer public health questions.[26] The dip in the number of Phase 1 trials in India in 2013 coincided with the overall reduction in the number of clinical trials. This is believed to have been as a result of regulatory reforms linked to hearings of a public interest litigation by the Supreme Court of India concerning clinical trials.[14] The Court's orders directing the government to frame additional rules came in the wake of irregularities highlighted in the conduct of clinical trials in the country. A series of regulatory notifications from the Indian regulator, the Central Drugs Standard Control Organisation, followed in compliance with these directions.[27,28] A steady rise in the number of trials in the years after this episode is a positive development for clinical research. Other measures that have helped spur trial registration activity include the publication of national policies and ethical guidelines that encourage trial registration and self-regulation by academic institutions and the pharmaceutical industry. India provides a good example of how clinical trial registration increased when appropriate measures were implemented.[29]

India still has a long way to go to catch up with the developed world in the conduct of clinical trials,[30] especially Phase 1 trials. It has been reported that the number of Phase 1 trials of cancer chemotherapy conducted in India between 2007 and 2017 did not match the late-phase trials of cancer chemotherapy undertaken in the country during the same period.[31] A similar picture might prevail in other therapeutic areas. Developing clinical trial capacity and capabilities within the country along all phases of the clinical development cycle is a pressing imperative given the growth and future of the domestic pharmaceutical industry, as much as it is so in view of the country's enormous disease burden and the potential therapeutic solutions that may emerge from its academic and research institutions. Acknowledging that Phase 1 clinical trials require special expertise and resources, various relevant academic organizations should be encouraged to upgrade and upskill to conduct such trials. India has the potential to emerge as a global hub for clinical trials, and sufficient regulatory provisions are in place to ensure the safety of the participants. What is required to fulfill this potential is an enabling regulatory environment, advanced training facilities in clinical drug development, and directed public funding to support innovation.[20,32,33]

Our study confirms that a majority of Phase 1 trials undertaken in the country were conducted in private nonacademic centers in Western India. The ICMR initiative to develop Phase 1 clinical trial units in academic institutions across the country is expected to respond to the need for the early-phase clinical trial facilities to develop therapeutic solutions in diseases of national health priority. On analyzing the data from ClinicalTrials.gov, we found that the number of Phase 1 studies undertaken in the United States by Indian companies from 2008 to 2022 was approximately a third of the total number of Phase 1 studies conducted in India in the same period. Discussion with industry stakeholders also indicates that many Indian pharmaceutical companies offshore their early-phase clinical trials. This points to the need to establish the

necessary capacity for early-phase drug development in India, and the need for a scientific and regulatory environment conducive to evidence generation for better therapeutics through such trials.

The major limitation of our study was the fact that there was no system to reconcile missing information on the part of the trial registrants. Notwithstanding this limitation, the review provides a comprehensive glimpse of all Phase 1 clinical trials that were registered to be conducted in India between 2008 and 2022.

CONCLUSION

A total of 220 Phase 1 clinical trials were registered to be conducted in India between 2008 and 2022. Most of the investigational products were drugs (55.0%) followed by vaccines (38.2%). The most common therapeutic class of drugs was cancer chemotherapy (19.8%), followed by antimicrobial chemotherapy and endocrinology (18.2% each). The most common vaccine was the influenza vaccine (21.4%), followed by the measles–mumps–rubella vaccine (15.5%). The pharmaceutical industry was the predominant sponsor for most (91%) of the Phase 1 trials. Most (31%) of the Phase 1 trials were conducted in three private nonacademic centers in Western India. There is an unmet need for Phase 1 trial facilities outside of the pharmaceutical industry framework to cater to academic research and therapeutic candidates that may emerge from publicly funded research institutions in the country. In this regard, ICMR is in the process of developing facilities in academic institutions that would be capable of planning and executing Phase 1 clinical trials of investigational products that are of national health priority.

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Conflicts of interest
There are no conflicts of interest.

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