CLINICAL TRIALS

With new regulations making the process cumbersome, clinical trials and research have come to a standstill in India

Clinical trials are critical to the development of new drugs: Health Minister J.P. Nadda
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TRIAL, AND ERROR

Complicated regulations and a cumbersome approval process are harming clinical trials and research in India

BY GUNJAN SHARMA

Cancer, for Kusum, shed its cloak of invisibility with a facial twitch in 2012.

The year was supposed to be one of new beginnings for Kusum and her husband, Vivek Tomar. Married for four years, the couple had been living apart owing to jobs in different cities—Vivek, a pharmaceutical graduate, had been working in Hyderabad, and Kusum was a schoolteacher in Rohtak, living with her parents and son. Gurgaon brought them together; they both found jobs here. They were out shopping, looking for furniture for their new home, when Kusum’s right cheek started twitching.

Kusum, 32, was initially diagnosed with tuberculosis of the brain. But her condition worsened after she started taking anti-TB medicines. Two months later, she was diagnosed with non-small cell lung cancer. “A radiologist saw a patch on Kusum’s lungs during a full body MRI scan. A rare form of cancer, it had already spread to her brain and formed multiple nodules there,” says Vivek.

Kusum underwent chemotherapy, but the drug reacted adversely
after the third chemo cycle. It led to accumulation of fluid around her lungs and almost choked her to death. "I am one of those few people who show resistance to chemotherapy. So, the doctors prescribed me the next line of drug—crizotinib," says Kusum. The drug kept the cancer under control for the next 22 months, but she developed resistance to it as well. There was no next-generation drug available in India, and without treatment, she was told she would live only for four more months. However, the drug she needed—ceritinib—was available in the United States. But importing it would have cost them ₹10 lakh a month, which was way beyond their means.

Vivek met doctors and wrote letters to various pharmaceutical companies to know how ceritinib can be brought to India at a reduced price. They told him that a drug could be brought to India only after it cleared the clinical trial phase here. The pharmaceutical company manufacturing the drug was awaiting the approval of the Drug Controller General of India (DCGI) to conduct trials. Vivek wanted to accelerate the process and he wrote to the DCGI. Finally, after four months, the clinical trials began and Kusum was put on the drug.

Kusum responded well to the drug. The tumours in her brain shrank. The cancer in the rest of the body was arrested and there was improvement in her condition. There were side-effects, of course—nausea, vomiting, drowsiness and epileptic convulsions. But she fought them all. A pink bicycle in the lawn stands testimony to her determination. When she started feeling weak, she asked Vivek to get her a bicycle so that she could build her stamina. "I want to live for my son and my husband. I can fight all odds to be with them," she says.

Kusum's cancer, however, continues to be invincible; she has developed resistance.

MUSICAL CARE: Meryl Mammen at her Ghaziabad home. She has Pompe disease, a rare disorder in which the body cannot make an enzyme required to break down the complex sugar glycogen.
PHASE 2
- Tests the efficacy of a drug
- Involves less than 100 patients
- Patients are randomly given either the new drug or a placebo
- Comparative information about the safety and effectiveness is derived

PHASE 3
- Involves 100 to 1,000 patients
- Provides thorough understanding of the effectiveness, benefits and possible adverse reactions
- On clearing phase III, the company can apply for marketing of the drug

PHASE 4
- Also known as post-marketing surveillance trials
- Monitors long-term effectiveness and impact on a patient’s quality of life
- Determines the cost-effectiveness of the drug therapy
- The drug may be taken off the market, based on findings in the study
Interview/Jagat Prakash Nadda, Union health minister

India-specific diseases need focused attention

BY GUNJAN SHARMA

How do you look at the process of drug development in the country?
Clinical trials are critical for development of new drugs. With increasing disease burden and emergence of new variants of diseases, some of which are specific to India, trials become all the more important. Development of new drugs for India-specific diseases is possible only through local research and clinical trials.

Besides, for us, it is important that drug development should be undertaken in an efficient and cost-effective manner while ensuring the rights, safety and well-being of trial subjects.

India has developed enormous capabilities in chemical synthesis, analysis and formulation development. India is one of the leaders in development of complex biological products such as pentavalent vaccine, pneumococcal vaccine, influenza vaccine, measles vaccine, rotavirus vaccine and hepatitis B vaccine. India has developed capabilities at a commercial scale to develop and produce rDNA products such as insulin, monoclonal antibody and blood products like albumin, which are produced at substantially lower costs. Medicines and vaccines developed in India are exported to more than 200 countries, including the US and Europe. We are working on vaccines for chikungunya and Zika virus.

How is the government planning to make clinical trials effective, quick and safe?

India-specific diseases need focused attention. At the same time, the government has been concerned about the infringement of the rights of patients and other trial participants. Keeping this in view, the Indian government has made it mandatory to provide for medical management and payment of compensation, which is not present in any other country. The effort has been to ensure patients' rights...
and safety and that there is no compromise in terms of the rigour of the trial.

India is the largest producer of drugs in the world. But new drugs take a lot of time to reach India. Why?

The clinical trial application processing was getting delayed. The government has carried out a careful analysis of the problems and issues involved and rationalised the processes. By doing so, it has been ensured that there is ease of doing business and the rights and welfare of participants in such trials are not compromised.

How are you planning to address the shortage of trained manpower in the regulatory sector?

India does not have a major deficiency of manpower in this area. However, it would be necessary to augment their skill sets. A series of training programmes of regulatory officials and experts involved in the approval of clinical trials and new drugs have been conducted to streamline the approval process.

During the last two years, major steps have been taken to enhance the regulatory capacity and a scheme for strengthening it has been approved at a cost of ₹1,750 crore.

Indian researchers say it takes months to get approval to conduct trials in India. Many a time, they fail to participate in global studies.

The government has taken a number of measures to promote the conduct of scientific and ethical trials in the country. In January last year, 25 panels, comprising nearly 350 experts for different therapeutic areas from government medical colleges and institutions, were approved. It helped in evaluation of applications of new drugs and clinical trials in a time-bound manner without compromising the quality of review.

Audio-visual recording of informed consent process is now mandatory only in case of vulnerable subjects in clinical trials of new chemical or molecular entity. Only audio recording is required in anti-HIV and anti-leprosy drugs...

An IT-enabled system for online submission and processing of clinical trial applications will be operational in a few weeks.

to ceritinib as well. She now needs the next line of drugs—alceatinib (available in the US market), brigatinib (cleared clinical trial) and lorlatinib (under clinical trial)—which are far from coming to India. “I can fight the side-effects and keep myself motivated, but how can I fight cancer without any drug?” asks Kusum. “There are so many advanced medicines in the US and so many more in the pipeline. The life-expectancy of someone with my kind of cancer is at least ten years. How can our government not think of bringing these lifesaving drugs to India when all other countries have them?”

Kusum’s story highlights the desperation of thousands of patients who live with diseases for which there are no medicines available in the country. It is ironical that the largest producer of drugs in the world finds it difficult to introduce new drugs in its own market. All because the process of getting permissions to conduct clinical trials—the only gateway through which a new drug can enter the Indian market after proving its efficacy and safety in the Indian population—is quite cumbersome.

After a drug molecule is tested in animals and found safe, the pharmaceutical company sends an application to the DCGI for conducting phase-I clinical trials. Once the approval comes in, the company chooses doctors as principal investigators, who are trained by the company on the protocols for the trial. The investigators give applications to the ethics committees, comprising groups of experts from various fields, of the clinical trial sites. The committee assesses the risks and benefits of the drug under study, and if found safe, grants permission for the four-phased trial. The investigator then enrolls patients and starts the trial. The sponsor of the study (the pharma company, in most cases), the DCGI inspectors and members of the ethics committee keep a close watch throughout the trial.

In India, clinical trials have lacked regulation for long. For nearly a decade till 2011, it was easy to obtain permission to conduct
clinical trials. According to the DCGI, the government approved 475 clinical trials for “new chemical entities”, not used as a drug elsewhere in the world, between January 2005 and June 2012. There were reportedly 11,972 cases of adverse effects excluding deaths, 506 of these being directly attributed to the trials. Besides, 2,644 deaths were reported between 2008 and 2013. Among them, four tribal girls, aged between 10 and 14 years, from Andhra Pradesh and Gujarat who died allegedly during the trials of a Human Papillomavirus vaccine for cervical cancer.

THE WEEK, in its cover story dated March 6, 2011, highlighted how the clinical trial industry in India had become a money-making business, which had led to the exploitation of poor and vulnerable patients. There were no stringent laws to guarantee adequate compensation to the patients in case of an adverse event owing to the drug under trial.

In 2011, many NGOs protested the malpractices prevailing in the sector. A petition was filed in the Supreme Court, which blamed the government for the laxity in the norms. In early 2013, the court appointed a committee, headed by Professor Ranjit Roy Chaudhury, a noted pharmacologist, to come up with recommendations to improve the system of drug development and clinical trials in the country. As per its recommendations, the permission of the health secretary had to be sought, apart from the DCGI’s approval for trials. However, objections were raised when the health ministry gave approval to 162 global clinical trials in less than two months the same year. Even as the government and court were charting out the new roadmap for clinical trials, many pharmaceuticals and research institutions like the US-based National Institutes of Health cancelled many of their trials in India.

Then came a set of new rules and regulations, which were anything but clinical. The regulations required registration of all ethical committees with the Central Drugs Standard Control Organization (CDSCO) of the Union health ministry, audio-visual recording of patients’ consent, involving insurance companies for providing compensation to patients in case of an adverse event and so on. “Everything came to a standstill for three years. It was a major setback for clinical research and new medicines in the country,” says Dr C.S. Pramesh, thoracic-onco surgeon at Tata Memorial Hospital, Mumbai.

Agrees Dr Vyankatesh Shivane, a diabetologist at KEM Hospital, Mumbai, who stopped conducting trials after the new regulations came in. “My private clinic was approved by the US Food and Drug Administration, but the new Indian rules are difficult to follow. I have conducted more than 45 trials, of which 12-13 drugs came to the market.”

Clinical trials are important to meet India’s requirements for new drugs for diabetes, he says. “Unlike the US, where insulin is the preferred line of treatment, people here want to delay its use. Besides, the patho-aetiology is
Positives of clinical trials

BY DR ANIL HANDOO

Carefully conducted clinical trials are performed to provide answers to questions such as: a) Does a treatment work? b) Does it work better than other treatments? c) Does it have side effects? They also provide information on the cost-effectiveness of a treatment, the clinical value of a diagnostic test and how a treatment improves quality of life. An unacknowledged benefit of clinical trials is the availability of an expensive new drug—available abroad as a standard of care for treatment but not yet approved for use in India—at no cost to the patient.

In May 2013, my mother-in-law was diagnosed with metastatic breast cancer, stage 4, positive of Her2-Neu and ER PR Negative. The treatment possibility had to include anti-Her2-Neu drug (Herceptin). The cost was high, but it was taken care of as she was a beneficiary of the Central government health scheme. Regular therapy helped control the disease, but it recurred after some time. The option now was T-DM1, available in India only as a molecule under trial. The drug was eventually available in the market, however at a phenomenal ₹2.5 lakh per cycle, to be injected every three weeks as long as one was alive or till one lost response. This would surely be an exorbitant amount for anybody and many would not even try this. Possibility of having the treatment as part of the clinical trial gives hope to many people suffering from such a disease.

While I do understand the negative aspects involving clinical trials, the possibility of making the drug available to many patients outweigh them. The need of the hour is to have a guarded yet favourable approach to clinical trials.

The writer is senior consultant and director of pathology and a member of the ethics committee at BLK Super Speciality Hospital, Delhi.

different. People with low body mass index also have high central fat,” says Shivane. “Cost is another major factor that pharma companies have to take into account before coming up with a new drug here.”

The most affected are cancer patients and people suffering from terminal illness, rare disorders, severe infections and drug resistance. The only way to deal with resistance to drugs and treat newer and rarer diseases is to build a parallel process of not only developing new drugs but making it available in the country. Take the case of Ghaziabad resident Shashank Tyagi, who has Gaucher’s disease, a rare genetic disorder caused by the abnormal buildup of fatty substance in organs. “I was bedridden and totally dependent on others for my daily chores. There was no drug to help me. When the clinical trial for enzyme replacement therapy was held in India, I enrolled myself. I am independent now,” he says.

Meryl Mammen, however, had trouble finding a suitable trial for Pompe disease, a rare disorder in which the body cannot make an enzyme required to break down the complex sugar glycogen. Enzyme replacement therapy, the only treatment available, costs ₹2.6 crore per year. “I would not have survived without medicine,” says the 26-year-old Ghaziabad resident. “My father’s company has been paying for my medicine for the last five years.”

Prasanna Shirol, founder of Organization
for Rare Diseases in India, says there are more than 7,000 rare disorders reported in India. Of these, drugs are available for only 500. “In Gaucher’s disease, for example, if 300 children are diagnosed, only 80 per cent can get medicine either through clinical trial or government aid. The rest suffer before they succumb,” says Shirod, whose 16-year-old daughter, Nidhi, suffers from Pompe disease.

Drugs in case of a rare genetic disorder may not cure but arrest the symptoms and help in improving the quality of life. In a standard process, it takes seven to ten years for a molecule to become drug and be available in the market after clearing clinical trials. People like Srinivas Birla of Mumbai are well aware of the consequences of such a long drawn-out process. Birla’s son Nihal lost his life to Hutchinson Gilford Progeria at 13. In the rare disorder, a child ages rapidly. There was no treatment available until a year ago, when he was called by Boston Children Hospital and Progeria Research Foundation to participate in a clinical trial in Boston for a new drug called Lonafarnib. The medicine worked wonderfully on him. Nihal got flexibility to bend forward and his negligible teeth line got its structure and colour back.

In March, however, Nihal died of dehydration. “He didn’t die of progeria,” says Birla. “The medicine under clinical trial improved his quality of life tremendously. I have decided that I will spread awareness about the importance of clinical trials so that parents of other children suffering from progeria do not say no to available medicine.”

From rare disorders to the most common infections, each disease is seeing a progression that is making it challenging for the medical fraternity to treat it.

Another important aspect of getting newer medicine is to reduce the cost of the treatment of chronic diseases. Dr Snatch Limaye, head of clinical trials at Chest Research Foundation in Pune, says 15 of 40 new molecules her institute conducted trials on in the last ten years have become the drug of choice in many cases. It is only because of research, says Limaye, that the cost of the treatment of chronic obstructive pulmonary disease, the second largest killer disease in India, has come down to 13 per dose.

“A doctor feels good when the molecule he or she has tested changes the life of the patients,” says Premesh. “Participating in a clinical trial is an additional responsibility for a doctor. Most doctors do it...
only when they are passionate about research. But it is necessary to have a population specific data for a drug to document its efficacy and safety in a particular population.

He cites the example of the global trial of Gefitinib, a drug for lung cancer, in which the Tata hospital had participated. “The drug was found to be ineffective in most countries. But while documenting the data, it was found that the drug was quite effective in a sub-group consisting of non-smoker Asian women. Though dismissed by the whole world, Gefitinib became the drug of choice for us in India,” he says.

In a survey conducted by Chest Research Foundation last year, most doctors who work as principal investigators in a clinical trial agreed on the central registration of ethics committees and on improving the mandatory compensation to the subjects for study-related serious adverse events. A majority, however, did not agree to making it compulsory to include government sites in clinical trials and the introduction of audio-video recording of informed consent. “Though the move to record the consent of the patient is to safeguard the patient’s right, it makes the whole process cumbersome. Patients get worked up and get suspicious about the safety of the trial,” says Limaye. “Besides, they generally have many personal queries regarding the side-effects of drugs on their sex life and child-bearing, which they are not comfortable asking about on camera and become reluctant in participating.”

The process of enrolling people in a clinical trial is different in India and the developed countries. In the US, the information about any ongoing or upcoming clinical trial is simply put on the institute’s website and around the campus. Interested patients themselves contact the doctor, who then explains the intricacies of the clinical trial. This way, patients have much more trust on the doctor. In India, it is the doctor who has to approach each and every patient.

The new guidelines unfortunately have also halted academic research in India. The Tata hospital, in collaboration with Medical Research Council, UK, was to begin research on how Aspirin, a popular blood-thinner, can be used as an anti-cancer drug. “There is a large data to support the initial research. It took both the institutes two years to draw all the protocols. Though the research has already begun in the UK, we are still waiting for the approval,” says Pramesh. “Can you imagine the impact this kind of a study will have in bringing down the cost of cancer treatment?” There is no comparison between cancer research in India and across the world, he says.

Even hardcore research institutes are finding it difficult to adhere to the government’s guidelines. Dr Raman Gangakhedkar, director, National AIDS Research Institute, Pune, says they have conducted eight to nine clinical trials.
few years ago when we had published our research work on identifying new anti-tuberculosis molecule, one of India’s leading national dailies printed it on the front page. The very next day, I got a call from a distressed husband, asking me if I could give that drug to his wife, whose tuberculosis was not responding to any other medicine. I had a hard time explaining to him that though there is a good science behind that new compound, I could not give it to any patient until it was tested, tried and approved by the drug regulatory body in India. The process, though crucial to establish the safety and efficacy of a medicine, is unfortunately cumbersome and time-consuming. Any molecule before it can become a drug for human consumption has to undergo a toxicology study, which then has to be tested on animals for its efficacy and then on a small population of humans before it could be marketed. Unfortunately, there is a substantial amount of risk capital required for this development phase. At present, researchers in India do not have much support in terms of logistics. Added to this is the lack of experience within the Indian community, which makes this entire process cumbersome. Clinical research is quite an expensive proposition with no instant returns. Obviously, it is a big decision for private pharmaceuticals to make an investment.

We, in India, are in desperate need of newer medicines for several infectious and parasit-
ic diseases such as tuberculosis and malaria. Ideally, the government should support such pathbreaking research through an innovative mechanism.

In the US, the FDA has a strict but simple process to grant permission to companies and researchers to carry out clinical trials. After a company submits its paper to the FDA, any objection has to come within a limited number of days. And in the absence of any objection, a company can go ahead with the clinical trials. The same approval in India may take several months to come.

While in the earlier era, owing to a different patent regime, we managed to compete in the prices of medicines, the same may not be true for the future. If we cannot accelerate the process of new drug discovery in India, we would be entirely dependent on the foreign companies and will have to bear a huge health care cost. This is the time when we should make every moment count.

The writer is director, Council of Scientific and Industrial Research-Institute of Genomics and Integrative Biology, Delhi.

Indian Council of Medical Research (ICMR), says she has been working towards bringing down the approval time for conducting a clinical trial to six months. Also, she says it is important to assess whether deaths and other adverse events related to clinical trials in the past occurred due to the drug under study or because of any other factor. “Take, for example, the HPV vaccine against cervical cancer. There were deaths reported in tribal girls in Andhra Pradesh. But it is important to take into account the death rate under the normal circumstances among the population under study,” she says.

Though it is important to make stronger rules to protect the rights of participants, Swaminathan says drug trial is equally crucial to protect people against deadly diseases. “We couldn’t participate in the global trials for multi-drug resistant tuberculosis of which South Africa was a part. Don’t we need newer drugs to address the growing problem of extreme drug resistant tuberculosis?” she asks.

Dr G.N. Singh, drug controller general of India, however, says the period of uncertainty and delay will be over shortly. The regulatory body is in the process of making the system of obtaining permission for clinical trials robust, fast and transparent. “Indeed, India has a unique disease burden and it needs to be addressed with country-specific drug trials. I think in the next two-three years, we should be back on track as far as clinical trials and bringing newer drugs to the Indian market is concerned.”

In early August, the CDSCO issued two circulars, giving the ethics committee the power to decide on the number of trials a principal investigator can undertake and also to choose the site of the trial. Earlier, an investigator could not work on more than three trials at a time, and only hospitals with minimum 500 beds were allowed to conduct trials.

Though these are steps in the right direction, it is high time India got clinical about drug trials.