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Review Article

EMERGING TRENDS OF SCOPE AND OPPORTUNITIES CLINICAL TRIALS IN INDIA

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ABSTRACT

India has emerged as one of the preferred destinations for the clinical trials of drugs by multinational pharmaceutical companies in recent years. The reasons for this include reasonably high standards of quality healthcare and healthcare professionals, use of the English language and the sheer size of target populations available in our country. Clinical trials are usually multi-centric but trials in North America and Europe turn out to be time consuming and expensive. While clinical trials in the west are not totally free from compromised interest, mishaps and litigation, the medical research organizations (MRO) are licensed and highly regulated and people are sufficiently aware of the possible risks of such trials and also aware of their rights to healthcare. In India, the scenario is very different. A non-uniform healthcare system, with varying standards in the government and private sectors, desperate poverty and lack of access to healthcare, illiteracy, lack of information and poor enforcement constitute a chaotic milieu which is a major challenge for a programme as critical as a clinical trial.

INTRODUCTION

India is emerging as a major centre for clinical trials in new products by multinational pharmaceutical companies. The country with a "diverse patient pool" holds good business potential in this field, say officials with pharma companies here. "Clinical research is emerging as a big business opportunity in India and hospitals in the country can take advantage of it," said Mr Patrick A. Floody, Manager Clinical Research, Pfizer Pharmaceuticals Inc. Recognizing this potential, several clinical research organizations (CROs) and multinational companies have already set up facilities for research in India. Besides the diverse patient pool, India also offers lowest per patient trial cost, said an official associated with clinical research in India. However, he said doctors in India generally spend less time with their patients as compared to their counterparts in other, particularly Western, countries. This could tell on the clinical reports. On an average, doctors spend only six to 10 minutes with a patient as against a desired 30 minutes. However, Mr Floody, who was earlier with Pfizer in India, said his company, which is conducting clinical trials in India, is quite satisfied with the investigators. He said the companies or the CROs should ensure that the investigators monitor patients as per their advice. It is said that there is a fear in India that in the absence of an adequate regulatory system for clinical trials, pharma companies may take advantage of the situation, treating innocent patients as guinea pigs. It is alleged that as most of the patients undergoing trials are illiterate, no adequate compensation or insurance cover is being given to them by CROs or the companies. But, according to pharma company officials, this fear is unwarranted as the Indian Government is soon expected to come out with laws governing clinical trials. Some guidelines are already in place. However, a practical problem in India is that several hospitals are not equipped with adequate and proper equipments to undertake clinical research in certain products. Speakers at a seminar on `Progress in clinical trials', organized by the Drug Information Association here, pointed out the need for proper and timely reporting of adverse effects of the drugs on trial. There are many advantages to choosing India as a location for conducting clinical trials. One company has recently expanded its operations there, so it can reap the benefits, which include lower costs and logistical access to the Asian market. Quest Diagnostics is one of the largest clinical diagnostic laboratories in the world. The company has bases in the US and UK and provides a full range of testing and clinical trial laboratory services to pharmaceutical and biotechnology clients across the world. Quest performs central laboratory services; it offers comprehensive laboratory testing and data generation for companies conducting clinical trials. One of the company's latest ventures is the setting up of a base in India for the provision of clinical trials services. Anthony J Santicerma, director of strategic alliances and global marketing at Quest, believes India has many advantages for his company.' There are the cost benefits, since labour in India is cheaper,' he says. 'By having a base in India makes sense from a logistics point of view, as samples do not have to be sent to laboratories in the UK or US for analysis. Furthermore, India has a highly professional workforce from which to draw personnel. More and

more clinical trials are now being staged in India because as a country with a growing economy there is a higher prevalence of Western diseases, such as the metabolic syndrome disorders of diabetes, obesity, hypertension and arteriosclerosis.' By expanding to India, Quest decided to establish its own laboratory and clinical testing base rather than use an affiliate company. The advantage of doing this is threefold according to Santicerma. 'First, is the advantage of having more control and the ability to make marketing and business decisions in order to grow both the international core diagnostics business and the clinical trials business, side by side,' he says. 'Secondly, the facility will provide a local laboratory to serve the entire region and will become a major hub for clinical laboratory services in Asia. Thirdly, by being in the area, Quest will be in a position to attract more business from local contract research organizations [CROs].'Another factor is the cost of bringing drugs to market, which, according to Santicerma, is increasing all the time. 'The cost of drug discovery and clinical trials is lower in India,' adds Santicerma. 'Estimates range from 30% to 70% lower than Western pharmaceutical companies. In the 1990s, little attention was paid to India because of limited protection for intellectual property. But now that it has more protection, gained through TRIPS [Trade-Related Aspects of Intellectual Property Rights], these cost benefits can be realized.' Conducting clinical trials in India is an average of 44% less expensive than conducting US-based trials, according survey data. A new study by pharmaceutical business intelligence leader Cutting Edge Information, "Streamlining Clinical Trials," finds that the average clinical trial costs pharmaceutical companies $125 million in the US compared to $70 million in India, on average. The report explores other reasons that companies outsource clinical trials as well -- cost savings is only one of many factors that help determine trial location. Other challenges in the US, such as patient recruitment and retention, have spurred companies to look for solutions outside of the US. In addition to India, other countries including Russia, China, and Brazil are all prime locations for clinical trials, in part due to improved trial conditions in those countries. David Richardson, project leader of the study said, "While cost levels of developing new drugs continue to rise in most geographic areas, companies are conducting clinical trials in India in order to conserve resources."Development of regulatory systems and research capacity strengthening cannot take place unless various stakeholders agree to some basic minimum rules. This process has begun as is evident from a recent workshop on clinical trials involving a rangeof stakeholders from the government, academia, industry and civil society held at the Administrative Staff College of India in October 2005, and a national conference on bioethics organized by the Indian Journal of Medical Ethics in November 2005,which included a component on clinical trials. Outsourcing of clinical trials to India is part of a larger globalization and knowledge economy process which, along with its potential benefits and downsides, seems set to proceed as the dominant theme of global development over the nearfuture.19, 20 Countries that draw up wise and innovative strategies to deal constructively with this seemingly inevitable shrinking of the world would stand the best chance of maximizing gains and minimizing losses from this process. As there is potential for mutual benefit, it would be desirable to capture the clinical trials' outsourcing opportunity in a manner that enables economic returns to India and the multinational companies, as well as tangible benefits to public health. These are not mutually exclusive if wisdom and foresight are exercised to develop the regulatory systems and indigenous research capacity required to keep these two objectives in balance. The public health situation in India is far from optimal, with a disproportionately high disease burden and a health system that is not effective in providing preventive and curative services to a large section of India's poor population, for which there are several systemic reasons.5–7 Health research, which generates knowledge to improve health, is not only meager overall in India but is also disproportionately low in public health and in several major diseases/conditions that contribute a large proportion of the disease burden.8 It would be undesirable if further distortions were caused by clinical trials research driven by multinational pharmaceutical companies without concurrent benefits to the health of Indians. Such distortions could occur due to various reasons. Drugs, vaccines and devices that undergo clinical trials in India may not be related to the major causes of disease burden here. Commercial pressures may lead to more emphasis on clinical trials for expensive therapeutic drugs than on preventive vaccines and cheap drugs. Ethical aspects related to human subject participation in research may not be fully addressed as the regulatory systems to monitor clinical trials are not in place in India, which may result in harm to participants of clinical trials. Although undesirable effects are possible, it would be unwise to ignore the potential benefits if clinical trials were to be enhanced appropriately in India. Besides attracting international investment, clinical trials could stimulate development of skills in clinical epidemiology and applied research, which are sorely lacking in India. The outsourcing of clinical trials to India is an opportunity which needs to be harnessed in a manner that yields improvements in the health of the population in India. For this to happen, two issues should receive attention, namely systems for regulation and research capacity strengthening. Indigenous capacity in the conceptual aspects of clinical trials' research needs to be strengthened in

India. This includes designing sound clinical research studies, advanced data analysis and scientific reporting of results. Two areas that need development of expertise are clinical epidemiology and biostatistics, which could be linked with the recent initiative to set up schools of public health in India.18 As pharmaceutical companies would benefit from this skills development in India, this is an opportunity for public–private partnerships to build research capacity in clinical epidemiology and biostatistics. This capacity building could be made sustainable if applied and public health research in India were planned strategically.6–8 With skills development in the conceptual aspects, clinical trials are more likely to address the major causes of disease burden in India than if multinational companies were to drive the design and thrust of clinical trials in India. This does not imply that collaborative efforts with multinational companies are not desirable, as these can be mutually beneficial if partnerships are equitable. An area that needs particular attention is the application of clinical trials' research tools to tap the vast potential of the traditional systems of medicine in India. Effective systems for regulation should include a national registry for all clinical trials, a competent approval procedure for clinical trials' protocols for new drugs and new uses of existing drugs, and implementation of rigorous ethical guidelines for clinical trials. The need for establishing registries for all clinical trials is now widely accepted to ensure complete reporting of both favorable and unfavorable results. This was highlighted by some recently reported major drug side-effects that went unidentified during the trial phases. The necessary but tedious task of setting up a registry in India would be facilitated if lessons learnt from the American and European experiences were assimilated and adapted to the Indian context. India has had its share of unethical and illegal clinical trials, and some unapproved trials may still be occurring. The regulatory authority that grants approval for clinical trials of new drugs in India is the Central Drugs Control Administration of India.

It is widely believed that the technical skills and administrative capacity of this authority must be enhanced substantially if an effective and efficient process for the scrutiny of clinical trial protocols were to become a reality. The quality and effectiveness of ethical review mechanisms for research on human subjects through Institutional Ethics Committees in India is highly variable. Mechanisms need to be developed for this system to be monitored by a competent national authority with powers of awarding penalties for violations. Testing of a new therapy or treatment trial progresses in an orderly manner which is known as phases. Which make researchers able to ask and answer questions in a way that results in reliable information about the drug and the patients. Clinical trials are usually classified into four phases.

PHASES OF CLINICAL TRIAL[2,3,4]

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV are 'post-approval' studies.

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies.

Pre-clinical studies

Pre-clinical studies involve in vitro (test tube) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.[15] Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement.

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay ranges from a small amount of money for a short period of residence, to a larger amount of up to approx $6000 depending on length of participation.

There are different kinds of Phase I trials:

SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the Maximum tolerated dose (MTD).

MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, whilst samples (of blood, and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

Phase II

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

- Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).
- Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design

Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized clinical trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Phase III

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIB studies."

While not required in all cases, it is typically expected that there be at least two successful Phase III trials,

demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), TGA (Australia), EMEA (European Union), or CDSCO/ICMR (India), for example.

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.[19]

Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Clinical trials phases[7,8,9,12]

There are three phases of clinical trials: Phase I, Phase II and Phase III. New drug treatments often begin with testing in a lab. Then they go through a Phase I trial, a Phase II trial, and finally a Phase III trial. If the trial results are good, the drug or other treatment may then be approved for use in the general public. In the United States, the Food and Drug Administration (FDA) decides whether to approve most drugs or treatments. Some types of treatment may not require all the phases of testing before being approved.

	Phase I	**Phase II**	**Phase III**
Description	A Phase I trial is the first test of a new treatment to see if it is safe to use in people. The new treatment is tested because it showed promise in lab tests.	Once a treatment is found to be safe (often in a Phase I trial), it can be tested to see if it helps patients.	A Phase III trial tests a treatment that has been shown to help some patients (often in a Phase II trial). It usually compares a newer treatment to the standard or best known treatment.
Goals	Learn: Whether the treatment is safe The best way to give the treatment (for example, as a pill or a shot) The right dose — the amount that causes the fewest side effects	Learn: Whether the treatment works Whether there are any less common side effects, which may appear when more patients get the treatment	Learn: Whether the new treatment is better than, as good as or worse than the standard treatment Phase III trials may be more complex and look at more aspects of treatment than Phase I or II trials.
Number of Patients	Often 20-30	Often 100 or more	Several hundred to several thousand
What to Expect	Patients often have many physical exams and tests (blood tests, for example) so doctors can find out how the treatment affects them. This may take a lot of time.	Patients often have many physical exams and tests (blood tests, for example). This may take a lot of time.	Phase III trials are usually randomized. This means half the patients in the study are chosen at random to get the newer treatment. The other half get the standard treatment. Patients and doctors do not decide which treatment the patient gets. As in Phase I and II trials, patients may have many physical exams and tests that may take a lot of time.

CLINICAL TRIALS IN INDIA: PATIENT AVAILABILITY[14,16,18]

Indian habitat is genetically more diverse than that of the western countries. A population of more than 1 billion makes India a very relevant place for conducting clinical trials. Moreover, India has a very large pool of variety of diseases cancer, diabetes, blood pressure and AIDS being the most common amongst them. Almost each family in India has at least one diabetic and one blood pressure patient. There is a bulk of patients who are willing to participate in clinical trials in India for common diseases as they are not so fatal. However, for fatal diseases like, cancer and AIDS also, people are participating in clinical trials in India. As, till now, there is no perfect cure for such diseases, people want to try and go for new and improved drugs in the hope of getting benefits from new medicines. People who are in critical stages of the disease mostly go for any hope that is capable of curing them. As there is a large population suffering from these disorders, clinical trials in India are always welcomed. Moreover, the drugs which are in trial stages are not expensive, this adds to the value of clinical trial drugs. As India is a developing country and majority of the population belongs to the middle income group, cheaper treatment is always preferred. India's pharmaceutical regulatory bodies are now even more mature to take care of the ethical issues related to clinical trials as the awareness level due to lack of literacy has not been very remarkable so far. Regulatory bodies are now much more experienced and careful for the consent forms and better understanding of patient and clinical trials in India. Regulation ensures that the patients are well aware of the clinical trials which they have to undergo and make the patient understand about the risks and benefits associated with the use of drug. In other words, their consent must be genuinely informed. India has the largest pool of patients with a variety of diseases. Asians are considered to have the most resistant immune system and hence the healthy volunteers are mostly not very sensitive for trial drugs that can lead to immediate adverse reactions. This is a boon to the companies who want to conduct clinical trials in India. Moreover, people are more participative owing to their need of cheaper treatment plus well trained doctors.On the other hand, China is a competitor of India in terms of patient availability and variety of diseases. But, the regulatory practices are not reliable enough to have a blind faith on patient availability. Hence, the ethical issues there are always doubtful.US comes under the list of developed countries and hence the scope of conducting clinical trials for pre approved drugs cuts down, as the people there are very conservative and not willing to take risks, especially when it comes to their health. They rely more on proven methods of curing diseases. Also, there is no such need of cheaper treatments and education. Thus, besides plethora of diseases found in the US, the clinical trials are not invited a lot.

CLINICAL TRIALS IN INDIA: TRAINED MANPOWER[22,23,24]

Highly skilled manpower is needed to conduct clinical trials and is the most crucial factor while carrying out a clinical trial. Let us compare and relate the manpower in the potential countries. India comes at the first place in terms of education and trained doctors when compared with US and China. The doctors of India are always in demand all over the world because of high standard of medical education in the country. Also, these doctors are trained to cure a wide range of diseases. Trained manpower is the key to success for Indian clinical research organizations. India has become a part of IPR regime and has passed the patent act. The academy of clinical excellence has added to the points of India's capability to conduct clinical trials. Moreover, doctors are well trained as per CDSO/GCP guidelines too. The 2005 amendment to the schedule Y of drug and cosmetic act is taking India towards acceptance of ICH guidelines for clinical research. China in this context is still in the developing stage for the regulatory issues and the trained manpower lags behind India. Moreover, the common language spoken is Chinese and not English. This is a major drawback for China.US equals India in terms of education and qualified doctors, but the points for skilled labor still go in the lap of India.

CLINICAL TRIALS IN INDIA: COST EFFECTIVENESS[25,26,,27]

Cost of conducting clinical trials in US is as follows:

Phase-1-$5404

Phase-2-$6538

Phase-3-$7635

Clinical trial for one drug in US costs approximately $1 billion. US infrastructure for conducting clinical trials is for sure unbeatable till now. While US continue to conduct clinical trials in flow, India and China are now seen as potential targets to conduct clinical trials. Potential contract research targets have been kept away from China owing to its week regulatory practices in the past, while with its recent entry into WTO; China is also considered as a platform for clinical research. China is a low cost hub for drug manufacturers. Indian infrastructure cuts down the cost of conducting clinical trials of new drugs to almost 60% of the cost in first and second world countries. The CRO business in India ranges between $100-$120m per year.. This is a huge factor which is making

the pharmaceutical countries flock towards Indian CROs manage many functions of a sponsor, monitoring the work in phase II-IV. Currently, there are almost 30 CRO in India. India gives a low cost advantage with high quality fast output. There has been a meteoric rise in the clinical research infrastructure in India as compared to early nineties, when there was negligible clinical research experience, improper documentation, poor infrastructure, and weak regulatory environment with non functional ethics committee. The potential for good practices is being realized now and clinical research facilities are being centralized in hospitals. Sites with well equipped laboratories and good research facilities allow the implementation of new and standardized policies. Simultaneously, with these new approaches, the interest of sponsors for clinical research in India is also developing at an accelerating pace. Above all, the investigators from different parts of the country are well trained in GCP compliant clinical research. Additionally, the availability of patients from different therapeutic areas and less time consumption add to the advantage of low cost clinical trials in India. There is a symbiotic relationship between the Indian infrastructure and clinical research. As, the Indian services are beneficial for clinical trials in terms of quality , training and costs, it adds more incentives to Indian platform when the sponsors provide highly sophisticated instruments to ensure good trial standards. The funds from sponsors are utilized to raise the standard trial sites.

CLINICAL TRIALS IN INDIA: TECHNICAL SUPPORT[23,24,25]

When we come to technical aspects of clinical research, the primary issues are:

It includes software development for electronic case report forms, data mining, data management, SAS programming and medical writing CRF and Database development. More than 500 companies outsource their software development to India as India is cost effective for the development of electronic data capture and e records of case reports forms.. Data mining is also a good outsourced business in India. While in US, the same quality of work is far more expensive, China is still in development phase of technology. Data management: Data management is done with technical expertise and under expert guidance in India with half the cost that in US. Statistical analysis and SAS programming: SAS has been expanding its applications in India. India has skilled and well trained programmers and is known for quality the world over. India being a pool of most skilled IT professionals, the country provides a strong IT support to clinical research. Indian industry is facilitating clinical research industry with new software solutions to streamline and integrate various functions of clinical research and that too at a very lower price as compared to US and China.

OPPORTUNITIES OF CLINICAL TRIAL IN INDIA[18,19]

In January 2005, the government of India enacted anew rule that allows foreign pharmaceutical companies and other interested parties to conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries. This new rule supersedes a directive of India's Drugs and Cosmetics Rules that required a"phase lag" between India and the rest of the world. According to the old rule, if a phase 3 study had been completed elsewhere, only a phase 2 study was permitted in India. Even under the new rule, phase 1 trials will not normally be permitted in India. The old rule was designed to protect Indians from being used as guinea pigs in the testing of unproved drugs of foreign origin; trials of domestically discovered drugs were not subject to this provision. The change was made in response to vociferous demands from multinational drug companies and private organizations that conduct clinical research for a relaxation of the rules for drug trials those necessary hurdles whose price tags can run to 40percent of the cost of drug development. It has become increasingly difficult to test drugs in Western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make the recruitment of research subjects slow and expensive. Consequently, many research-based companies are now outsourcing some of their trials to Third World countries such as China, Indonesia, Thailand, and India. India is a particularly attractive site for such trials because of its genetically diverse population of more than 1 billion people who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders. Virtually all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily in Britain or the United States. Added to these attractions are cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by as much as 60 percent. However, even from the viewpoint of foreign drug companies, there are some major drawbacks to working in India. Sponsors do not have exclusive rights to the clinical data they generate: because trial reports are in the public domain, manufacturers of generic drugs can use the data to obtain regulatory approval of their own versions of a drug. Furthermore, the Drugs Controller General of India (DCGI) the equivalent of the U.S. Food and Drug Administration (FDA) is understaffed and lacks the expertise to evaluate protocols. Currently, the technical staff consists of just three pharmacists, including the controller, and not one medically qualified doctor. As a result, persistent follow-up, including personal visits to the DCGI, is required in order to push an application for a trial forward. In addition, although the country has more than half a million practicing doctors, fewer

than200 investigators have been trained in good clinical practice. Among some 14,000 general hospitals, no more than 150 have the adequate infrastructure to conduct trials, and there are fewer than a dozen pathology laboratories that meet the criteria for compliance with good laboratory practice. Only about half of the large hospitals have institutional review boards, and even these boards have not yet formulated standard operating procedures and they, too, often lack the expertise with which to evaluate protocols. Information about conflicts of interest is neither sought nor voluntarily provided by investigators. Given the sorry state of the apparatus for reviewing proposals, the greatest concern about clinical trials in India, from the vantage point of both India and other developing countries. A notable example was a study, conducted in the early 1960s, of new regimen for home based treatment of tuberculosis, which was sponsored by the World Health Organization, the British Medical Research Council, and the Indian Council of Medical Research.4Nevertheless, even as corporate sponsors, clinical research organizations, investigators, and hospitals demand easier access to Indian subjects for studies of new foreign drugs, opponents argue that India itself would not benefit greatly from these studies. The first reason it would not benefit is that the much-hyped earning potential is likely to remain a distant dream. Last year, although U.S. companies spent a total of $33 billion on new-drug research, U.S. and other Western companies combined spent only $30 million in India. Even with relaxed rules, India makes as much in one day by exporting computer software (which offers no direct risk to anyone's health) as it can in a year by offering up its citizens as study subjects. Second, according to the FDA, no more than 20percent of the drugs introduced during the past decade have been breakthrough agents. The rest represent marginal improvements over existing therapies that are more expensive than the older drugs and are often aimed at extending the patent life of free of charge after completion of the trial, if it is found to be beneficial. There have, of course, been some ethical and a therapy without offering any major new benefit for patients. Although this issue arises even in the developed world, it is of particular concern in countries like India the poor in the Third World should not be used to establish the "safety and efficacy "of such products. Moreover, if trials are used to promote drugs that are more expensive but neither more effective nor safer than the standard treatments, the result is higher overall costs for health care and poor patients paying more for equivalent therapies. Third, the sponsors do not guarantee that new drugs tested in India will be made available there at affordable prices. Recent examples suggest that new patented drugs will cost so much that most Indians will not be able to buy them. For example, EliLilly plans to price just one 10-mg tablet of tadalafil (a treatment for erectile dysfunction) at $9 (400 rupees), which is equivalent to four days' wages fora well-paid manual worker.5No one disputes that researchers should be encouraged to conduct Indian trials of new drugs for diseases that are endemic to this country, such askala-azar (visceral leishmaniasis), leprosy, trachoma, tuberculosis, and water-borne diseases. But to our knowledge, hardly any trials involving such new drugs have taken place in India; globally, only1 percent of the new drugs discovered in the past25 years have been for tropical diseases. Moreover, even before such a limited form of "liberalization, "or opening of the economy, occurs, adequate safeguards must be put in place to protect participants. Such safeguards might range from a procedure for the proper review of study protocols by the DCGI to the registration of trials and their results on publicly accessible Web sites to requirements for insurance and appropriate compensation of subjects in whom the drugs under study have adverse effects. Real informed consent should be obtained from participants in the presence of an objective third-party. Trials should be conducted only by investigator strained in good clinical practice at designated research hospitals. Truly independent institutional review boards should be formed, and a system should be created to enable these boards to share information about trials they have rejected and their reasons for doing so. All projects should be carefully scrutinized for their value to the Indian people. In a population such as India's, a large proportion of the subjects in any trial will inevitably be disadvantaged persons. It is therefore of paramount importance to protect the most vulnerable women, children, the poor, and the illiterate by making sure that their enrollment in trials is truly voluntary and that their consent is genuinely informed. They should have access to the drug after the trial if it is found to be effective, and they should not only be treated and compensated for injury but also be compensated for any resultant loss of income. These things can be done only when the government has strengthened its regulatory system so that it is geared toward guarding the rights of patients and protecting them from exploitation.

SCOPE AND IDEAL DESTINATION OF CLINICAL TRIAL IN INDIA[22,23,24]

The last 10 years have been witness to an increasing number of clinical trials conducted in India. Indian pharmaceutical companies are investing higher amountsin R & D as they nurture global ambitions. Significantly, many multinational pharmaceutical companies areeyeing the opportunities available in India to augment their R & D productivity. The result has been anexponential growth in the number of clinical trials conducted in India. This growth is mirrored in large measure by the increase in the debate on the ethics of such trials in India. A number of commentators, in India and abroad have alluded to the participation of Indians in clinical trials as the "guinea

pig syndrome". Though the debate has been good to bring clinical trials into limelight, it is also responsible for shaping the attitudes of most Indians towards clinical trials. Any ambiguity about the role of such clinical trials in our society reflects the confidence (or lack thereof) we repose in the process for development of new drugs. Imagine a patient who goes to his doctor looking for a cure. A clinical trial, simply put is an experiment conducted to study if a new medication is safe and effective in the treatment of a particular medical condition. Because not much is known about the new medication at the time of a clinical trial, doctors are required to follow a rigorous schedule to oversee patient safety. Patients may be required to follow-up with the doctor more often than in routine practice and the doctor's team is expected to spend much more time with the patient than in routine practice. This usually works to provide much more stringent oversight for patients in a clinical trial than they might have access to otherwise. The premise of any clinical trial is the "principle of essentiality" elucidated by the Indian Council of Medical Research. A clinical trial is done, simply because, it needs to be done. If other methods were available to evaluate new medicines, scientists and governments would be more than happy to use those for evaluation of new agents. However, even though a number of initiatives are being explored to reduce the number of patients exposed to new clinical trials, the fact remains that the clinical trial remains the most robust way to evaluate new agents today. It's also important to appreciate that modern medicine, though highly evolved, is yet an imperfect science. To quote a recent Business week story "From heart surgery to prostate care, the health industry knows little about which common treatments really work". Most medicines used today offer significant alleviation of suffering in relative terms, but in absolution, modern drugs suffer from safety and efficacy issues. Scientists and doctors over the world continue the search to understand which treatments are safer and better for their patients. Sowhen a doctor offers to enroll a patient into a clinical trial; he's really requesting the patient's collaboration in an experiment to further the understanding of medicine. The objective is to allow patients access to better medicines in the future to come. Each clinical trial is conducted in four phases. The Food and Drug Administration (FDA) must approve each phase before the study can continue.

Phase I: In this phase, a new drug or treatment is tested on a small group of healthy people to determine safe dosage, study how the drug works in the body, and see if it has any side effects. The overall safety of the drug is not known during this phase.

Phase II: The drug or treatment can now be tested on a larger group of people to see if it is effective and to further test its overall safety. Rating scales are developed and used to record data during this phase.

Phase III: Now the drug or treatment is ready to be tested on even larger numbers of people. The study will look even more closely at the drug's effectiveness, if it has any side effects, overall safety, and how it can improve a person's quality of life. Most drugs that reach this phase are considered for FDA approval.

Phase IV: Once given FDA approval, the trial can enter into the final phase, which involves monitoring the drug after it has been released to the public. In this phase, researchers look for additional information such as risks, benefits, and optimal or additional uses of the drug. In some cases this phase is used to test the drug on a sub-group of people (such as patients over a certain age).

India is fast-emerging as an attractive destination for clinical trials. Today, the market value of clinical research outsourced to India is estimated at US$100 million. A clinical trial is a costly as well as time-consuming process. The cost of conducting clinical trials for a specific drug ranges between US$350 and US$500 million. Now about 20 organizations in India specialize in clinical trails. These companies have the skills to comply with standards such as ICH-GCP guidelines. Currently, 20 to 30 per cent of the clinical development activity is outsourced to Clinical Research Organizations (CROs) in developing countries such as India due to lower costs. The cost of conducting clinical trials in India ranges between 20 and 60 per cent of the cost in western countries. According to industry sources, a volunteer in a developing country is paid between US$70 and US$350, based on the nature of the study, for participating in three studies a year. By contrast, volunteers in western countries are paid relatively higher amounts. Not surprisingly, research-based global drug companies are keen to outsource clinical trails to developing countries such as India. Today, about 80 government and private hospitals in India are engaged in global and local clinical trials. Multinationals drug companies are also entering India, drawn by the vast pool of scientific talent. The multinationals in the CRO segment include ICON Clinical Research, Omnicare Clinical Research, Pharmanet global, Pharm Olam, ClinTec International and Quintiles Spectral. The Indian clinical market is likely to be worth US$1.5-2 billion by 2010, provided the number of patients in Indian trial sites constitutes 20 per cent of patients in global clinical trials. This report provides an in-depth understanding of clinical trials in India. While front-end sections such as Executive Summary and Highlights provide the essence of the report in a few pages, the remaining part of the report provides an exhaustive analysis of clinical trails in India. The middle of the report focuses on market scenario and major players. It also comprises an in depth analysis of the growth prospects of the industry.

The report also covers issues such as technology, growth factors and critical success factors. The regulatory framework, under which the trials are conducted, is discussed briefly. The report also comprises a separate section on the issues and challenges confronting CRO's. The end section of the report contains an outlook for clinical trails in India besides utilities such as glossary. In the outlook section, the report builds upon the information and analysis of the previous chapters to forecast future trends. Life Sciences companies and the companies, which provide services to life sciences companies, will find this report useful.

This report provides a deep understanding of clinical trials in India. Clinical research Organizations (CROs) in India, which are already engaged in clinical trials, will find this report useful in putting their performance in perspective and fine-tuning their strategies as well. For companies planning to enter the clinical trails segment, this report will provide an overview of the current situation and issues that may crop up in the latter part of the trials. Bioservices, which is the fast-growing segment in the industry, is also covered in the report. This report will be useful to companies engaged in biotech services. It will also help Doctors (Investigators), the sponsors of trials and drug companies. Students, who plan to get into clinical trials, will certainly benefit from this report. The drug companies may use this report as a ready reckoner and a source of latest information. It might take somewhere between 10 and 15 years for the drug development process from pre-clinical to complete phase III clinical trials. Out of which, the phase II and III clinical trials consume almost half of the time. Given this situation, it looks imperative that pharmaceutical and biotechnology companies ought to look for ways to conduct trials faster and with less spending. However, they have often failed to meet the challenge and hit the market with the drug as planned. The reasons have been the dropping enrollment for clinical trials in the US and Western Europe and that has led companies to think of alternative places where they can have trial sites and which can help them enroll more volunteer to conduct trials faster. The recent attentions of the companies have been to look forward to the countries like India and China as a solution. It is believed that one of the advantages of conducting clinical trials in areas such as Eastern Europe and Asia is the speed at which patients can be recruited; as it is very difficult to get patients to enroll now in the U.S. Enrollment rates in the Far East and China and Eastern Europe and India are much faster. So, if you needed 200 patients for an oncology trial, your chance of getting them in India within a three-month enrollment period is much higher, whereas it might take you a year or more in the US. While there have been a number of challenges to conducting these clinical trials, several countries, most notably India, have taken a number of steps to make the process more user-friendly. In 2005, the Indian government increased intellectual property protection on patents, a key change in a country's enforcement of laws protecting patents and clinical trial data. That made companies a little more comfortable coming to India. Another legislative change was for sweeping, mandatory global clinical practices for conducting trials.

But one of the most important legislative changes has been the amendment of schedule Y of the Indian Drugs and Cosmetics Act to comply with the regulations of the International Conference on Harmonization. Prior to the amendment, there was a phase-lag rule in effect that barred earlier-phase trials from being conducted in India before being conducted elsewhere in the world. "What that did is, it said, if you're doing a trial in India, you need to be one trial further advanced in the rest of the world. So if you were doing a phase III trial in Europe, you could do phase III trials in India, but you could not do phase II trials, and that was really to protect the country." The amendment means companies can include India in global, multi-center trials in all phases. That allows companies to conduct their clinical trials more quickly and efficiently. Many pharmaceutical and biotechnology companies are turning to CROs like Quintiles and Accenture to take their trials outside the US and Western Europe. Similarly many of the CROs are specialized now operating in Indian subcontinent because of local geographical knowledge. Certainly India becomes the more obvious choice because it is home to over 16,000 hospitals and 500,000 doctors, making it an ideal country in which to conduct clinical trials. Whereas one of the challenges of conducting clinical trials in China is that simply getting a clinical trial application approval can take from seven to 10 months.clinical trials market in India is estimated at $200 million and is expected to grow to $1 billion by 2010.The market has grown at almost 400 per cent in the past two years and is pegged to grow even more by 2010. Currently, India has a global market share of almost 50 per cent in the clinical trials business. It might take somewhere between 10 to 15 years for the drug development process, from pre-clinical to complete phase III clinical trials. Out of which, the phase II and III clinical trials consume almost half of the time. Given this situation, it looks imperative that pharmaceutical and biotechnology companies are ought to look for ways to conduct trials faster and with less spending. However, they have often failed to meet the challenge and hit the market with the drug as planned. The reasons have been the dropping enrollment for clinical trials in the US and Western Europe and that has led companies to think of alternative places where they can have trial sites, and which can help them enroll more volunteer to conduct trials faster. These companies are looking forward to the countries like India and China as a solution. It is believed that one of the advantages of conducting clinical trials in areas such as Eastern

Europe and Asia is the speed, with which patients can be recruited. As, it is very difficult to get patients to enroll now in the US, enrollment rates in the Far East, China, Eastern Europe and India are much higher. So, if you needed 200 patients for an oncology trial, your chance of getting them in India within a three-month enrollment period is much higher, whereas it might take you a year or a year and a half in US.While there have been a number of challenges to conducting these clinical trials, several countries, most notably India, have taken a number of steps to make the process more user-friendly. In 2005, the Indian government increased intellectual property protection on patents, a key change in a country's enforcement of laws protecting patents and clinical trial data. That made companies a little more comfortable coming to India. Another legislative change was for sweeping, mandatory global clinical practices for conducting trials. But, one of the most important legislative changes has been the amendment of schedule by the Indian Drugs and Cosmetics Act to comply with the regulations of the International conference on harmonization. Prior to the amendment, there was a phase-lag rule in effect that barred earlier-phase trials from being conducted in India before being conducted elsewhere in the world. "What that did is, it said, if you're doing a trial in India, you need to be one trial further advanced in the rest of the world. The Indian government is increasing its surveillance of clinical trials, and has announced plans to set up a registry of trials and create legislation to enforce ethics guidelines. The move comes in response to years of controversy over unregulated trials. Clinical trials are highly profitable for India in 2003, the country earned US$17 million in revenue from them. But, although international collaborators are keen to do more trials in India, delegates at a private conference on India's capacity to conduct such trials last week said that the country is not ready for this expansion. At the conference, the health ministry announced it had begun training inspectors to audit trials. A survey by the Indian Council of Medical Research earlier this year showed that only 40 of 179 institutional ethics committees follow ethics guidelines. Although the rules were drafted more than five years ago, there is no legislation to enforce them.India's drug controller has said that strict regulation of clinical trials would not be easy because the country does not have " a culture of policing doctors".

BOOMING CLINICAL TRIALS MARKET IN INDIA[12,13,14]

India to Conduct 5% Global Clinical Trials by 2012 India is fast emerging as a preferred destination for conducting global clinical trials due to multiple reasons and is forecasted to conduct around 5% of the global clinical trials by 2012. India is fast becoming one of the biggest hubs for conducting global clinical trials. In 2007, the country conducted around 220 clinical trials, making up for less than 2% of the global clinical trials But according to "Booming Clinical Trials Market in India", a new research report by RNCOS, a number of factors such as low cost, large patient pool, easy recruitment, strong government support and strengthening of its intellectual property environment will enable India to conduct nearly 5% of the global clinical trials by 2012.

As per the report, India scores well above many other destinations in almost every factor analyzed. For instance, India provides one of the largest patient pools for both infectious and chronic diseases. Moreover, the country has 40 million diabetics, representing the largest in any country. Similarly, India also has one of the highest numbers of patients for other chronic diseases such as cardiovascular, neurological disorders, respiratory disorders and obesity. Apart from chronic disorders, the country also provides one of the largest numbers of patients for such infectious diseases as HIV, malaria and tuberculosis.

The findings of the report suggest that not only does India provide a large patient pool, the recruitment of these patients is also among the fastest in the world. As most of the healthcare costs in India are paid "out of pocket", a large patient population continues to have unmet medical needs. As a result, they readily volunteer to participate in clinical trials to get free treatment.

"Booming Clinical Trials Market in India" gives an extensive and objective analysis on the Indian clinical trials market. It investigates the advantages and disadvantages India has over other countries to become a global clinical trials hub. The report exhaustively evaluates and compares the key factors that drug companies and CROs look before outsourcing clinical trials to a country. These include factors such as patient pool, regulatory environment, cost, infrastructure, human resources and past performance in conducting clinical trials. Thus, the report serves as a useful guide for drug manufacturers, CROs, consultants and investors who are planning to enter the Indian clinical trials market.

CLINICAL TRIALS MARKET OPPORTUNITY IN INDIA[25,26,27]

- The Indian Clinical Trial Market is estimated at $100mn with the prospects of reaching $300mn by 2010
- The market for Clinical trials is growing at 30-35%
- The Market has grown rapidly in the period 2000-2005 and is made up of more than 30 companies. International and Domestic CROs are equally represented

❖ The change in country's property laws has enabled the growth in the Indian market for clinical trials

❖ As per an estimation study by the Global consulting firm McKinsey & co European and US pharmaceutical companies will spend US $1.5bn per year on Clinical trials in India by the year 2010

❖ Today 122 clinical trials are being conducted in India

❖ Glaxo SmithKline, among the world's top ten Global pharma majors is carrying out the largest number of Clinical Trials in India

❖ Apart from the development of Vaccines, Glaxo is conducting 13 Drug trials in India for the treatment of Diseases such as Cancer, Arthritis, Epilepsy, Heart Disease and Constipation. These include Phase II, III as well as Phase IV clinical trials

❖ Astra Zeneca is the other Global Pharma company outsourcing a significant number of its Trials to India

❖ Out of the 186 Clinical Trials that Astra Zeneca is doing Worldwide about 9 have investigation centers in India. These studies include drug trials for schizophrenia, bipolar disorder, cancer, diabetes and testotoxicosis, CNS, Cardiovascular, oncology and are conducted on adults and in some cases on children

❖ Johnson and Johnson and Eli Lilly are each conducting studies on 8 drugs trials in India while Pfizer is conducting 7 drug trials

❖ Some of the other MNC Drug majors conducting trials In India are Sanofi-Aventis, Merck, Wyeth, Bristol-Myers Squibb, Roche, Novartis

❖ Moving these trials to India translates into saving time for the pharma companies who are looking to develop the next blockbuster drugs i.e Drugs with annual global sales of $1bn

❖ India with a population of 1 bn has a broad spectrum of diseases. There is a high incidence of infectious diseases such as TB, malaria, AIDS/HIV, Multidrug-resistant pneumonia, Hepatitis B and readily available patient populations

❖ India has the diseases of the tropical world plus diseases of the developed countries

❖ The Patient populations for many chronic and western diseases such as Type-2 diabetes, cardiovascular disease, depression and many forms of cancer and CNS diseases are largely growing(India leads the world in the Type-2 diabetes patients)

❖ Due to the high population density of urban areas that have few, but large hospitals, in the limited number of trials conducted, most of the MNCs have been able to recruit a large number of patients quickly

❖ The recent global guidelines make it mandatory to test new drugs across a variety of new gene pools.

❖ It is easier to do multi-centric large-scale trials in India for many diseases, since the patients' enrolment rate for phase III studies can be up to six times higher in India than US or Europe and high incidence of infectious and life style disorders provide large number of patients for Clinical trial

❖ Clinical Trials in India cost 50-60% less than the average cost in US and other developed markets largely due to significant reduction in the costs of patient recruitment and medical personnel, which account for about 70% of the total clinical costs

❖ The cost of trials in India is 50% lower than the $20mn required in the US for Phase-I study and 60% lower than the $50mn required for the phase-II study

❖ According to an estimation done by Glaxo SmithKline, its cost savings per person for clinical trials shifted to India is in excess of $10,000

❖ Quality of the trials conducted in India is consistently rated as comparable or superior to US/EU trials

❖ Indian companies like Ranbaxy, Sun Pharma, Cadila, Nicholas Piramal, Lupin have set up world-class clinical research faclities to bring the drug from mind to market

ADVANTAGE OF CLINICAL TRIALS INDIA[12,13,14]

❖ Well-trained medical community to global standards.

❖ Wide spectrum of diseases, with low per capita drug expenditure.

❖ Huge patient base

❖ Heterogeneous population base

❖ High enrolment rates

❖ Large and fast growing private healthcare sector

❖ State-of-the-art hospital faclities

- ❖ Government commitment to provide Intellectual Property Protection from January 2005 - transition already in progress.
- ❖ Proposed changes to regulatory policies to facilitate clinical research.
- ❖ Lower costs for clinical researchers, nurses, IT staff, along with reduction in patient-related costs
- ❖ Diversity in India's gene pool
- ❖ Difficulty in recruiting for trials globally. India has adequate patients and investigators
- ❖ Overall lower costs for conduct of trials.
- ❖ Rapidly increasing awareness of ICH-GCP(The International conference on Harmonisation- Good Clinical Practice) guidelines for conduct of clinical research
- ❖ English as a primary language of education and communication
- ❖ All investigators speak English and GCP trained investigators are increasing in number
- ❖ Education level of the clinical researchers in India is quite high
- ❖ Increasingly accommodating regulatory environment
- ❖ The new IP regime as of 2005 provides a greater level of comfort level with doing clinical research in India
- ❖ Communication and IT infrastructure and capabilities are at Western standards
- ❖ Support services such as Clinical data management
- ❖ Data generated in India is accepted by all major conferences and journals
- ❖ Import duties on clinical material has been eliminated

CONCLUSION

New medical treatments must be proven safe and effective before they can be offered to a large number of patients. New treatments are tested through clinical trials, a series of research studies using a limited number of patients. Any new type of treatment can be tested in a clinical trial. For example, when doctors use a marrow or cord blood transplant to treat a disease not usually treated with a transplant, that transplant is usually done as part of a clinical trial. Many transplant patients take part in clinical trials that test drugs used prior to transplant or to stop infection or fight graft-versus-host disease (GVHD) after transplant. Most patients who receive an unrelated donor transplant have the option of taking part in a clinical trial at some time during their treatment. If you are thinking about being in a clinical trial, you should learn all you can about the trial you are considering. You should also learn about how clinical trials work.A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work. Once researchers test new therapies or procedures in the laboratory and get promising results, they begin planning Phase 1 clinical trials. New therapies are tested on people only after laboratory and animal studies show promising results. All clinical trials are based on a set of rules called a protocol. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of the treatment. Clinical trials of experimental drugs proceed through four phase. In Phase 1 clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase 2 clinical trials, the study drug or treatment is given to a larger group of people (40-100) to see if it is effective and to further evaluate its safety. In Phase 3 studies, the study drug or treatment is given to large groups of people (more than 200) to further determine its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Phase 4 studies are done after the drug or treatment has been marketed. These studies continue testing the study drug or treatment to collect information about their effect in various populations and any side effects associated with long-term use. The government has strict guidelines and safeguards to protect people who choose to participate in clinical trials. Every clinical trial in the United States must be approved and monitored by an Institutional Review Board (IRB) to make sure the risks are as low as possible and are worth any potential benefits. An IRB is an independent committee of physicians, statisticians, community advocates and others that ensures that a clinical trial is ethical and the rights of study participants are protected. By federal regulation, all institutions that conduct or support biomedical research involving people must have an IRB that initially approves and periodically reviews the research. All clinical trials have guidelines about who can get into the program. Guidelines are based on such factors as age, type of disease, medical history and current medical condition. Before you join a clinical trial, you must qualify for the study. Some research studies seek volunteers with

illnesses or conditions to be studied in the clinical trial, while others need healthy volunteers. Healthy volunteers participate in Phase 1 trials, some vaccine studies and trials on research on preventive care for children or adults. The factors that allow you to participate in a clinical trial are called inclusion criteria and the factors that keep you from participating are called exclusion criteria. It is important to note that inclusion and exclusion criteria are not used to reject people personally. Instead, the criteria are used to identify appropriate participants and keep them safe. The criteria help ensure that researchers will be able to answer the questions they plan to study.The clinical trial process depends on the kind of trial in which you participate. The team will include doctors and nurses as well as social workers and other health care professionals. They will check your health at the beginning of the trial, give you specific instructions for participating in the trial, monitor you carefully during the trial, and stay in touch with you after the study.Some clinical trials involve more tests and doctor visits than you would normally have for your illness or condition. For all types of trials, you will work with a research team. Your participation will be most successful if you follow the protocol carefully and stay in contact with the research staff.

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