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AHMEDABAD, GUJARAT

ESSAY COMPETITION-2016

ON

**“CLINICAL TRIALS IN INDIA AND CHINA:
ADVANTAGES AND DISADVANTAGES”**

Essay Competition - 2016

Subject

“CLINICAL TRIALS IN INDIA AND CHINA: ADVANTAGES AND DISADVANTAGES”

Number of Entries
16 from all over India

Panel of Judges

Dr. Shiv Prakash Ratnam
CEO, Synchron Research

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Winners

GOLD MEDAL

Mr. Devendra Pratap Singh
Doctoral Student
B. V. Patel PERD Centre, Ahmedabad.

SILVER MEDALS

Esha Hiten Shah
Masters in Pharmacy (M.Pharm)
Bombay College of Pharmacy
Kalina, Mumbai.

Mr. Swapnil Purushottam Borse
Doctoral Student
B. V. Patel PERD Centre
Ahmedabad.

FIRST PRIZE (GOLD MEDAL) - 2016



Mr. Devendra Pratap Singh

Mr. Devendra Pratap Singh is currently pursuing Doctoral Research at Department of Pharmacology, B. V. Patel PERD Centre, Ahmedabad. He and his team has pioneered the work of NSAID-induced gastroenteropathy in India. In this purview, they developed a novel model for NSAID-induced gastroenteropathy, deciphered novel target based pathogenesis, identified novel anti-TNF agents for its efficient management and filed a patent for few of them. For unravelling the novel therapeutic strategies for NSAID-induced gastroenteropathy, he was awarded prestigious G. Achari Prize. His current focus is to develop novel drug delivery systems for the management of NSAID-Gastroenteropathy by applying Quality by Design. He is Recipient of Prime minister Scholarship, 6 consecutive academic excellence awards, 1 Gold medal and many best oral and poster presentation awards. He has 5 high impact international research publications, 1 patent and many oral/poster presentations to his credit.

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Essay Competition 2016 ➡ 3

SECOND PRIZE (SILVER MEDAL) - 2016



Esha Hiten Shah

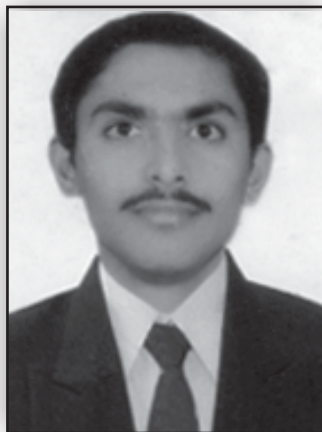
Pursuing Masters in Pharmacy (M.Pharm) in the Department of Pharmaceutical Analysis from Bombay College of Pharmacy, Kalina, Mumbai.

Working on a project titled “Analytical method development of a Proniosomal formulation” under Dr. (Mrs) Vaishali A. Shirsat.

Achieved various accolades over the years for Essay and debate competitions.

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SECOND PRIZE (SILVER MEDAL) - 2016



Mr. Swapnil Purushottam Borse

Mr. Swapnil Purushottam Borse is currently pursuing Doctoral Research (establishing disease timeline for personalized integrative medicine- Diabetes a case example) at Department of Pharmacology & Toxicology, B. V. Patel PERD Centre, Ahmedabad. He strives on new challenges & feels very strongly that research should be as integrated as possible. He accept that, as we move ahead the subject boundaries vanishes and hence he is successfully correlating Ayurveda and modern science at their fundamental levels on the basis of cocktail knowledge of Pharmaceutical sciences and Ayurveda. He and his team have pioneered the work of *AyurnizationTM*, NSAID-induced gastroenteropathy; deciphered novel target based pathogenesis of gastroenteropathy and diabetes, and also identified novel anti-TNF agents for efficient management. He is extensively working on personalized-integrative medicine. He has published 6 articles, 7 oral/poster presentations at national international level (with best poster award in two). He has filed 2 patents and 2 trademarks to his credit. He also serves as an advisor to Mendeley. He is approved mentor at AuthorAid. He is reviewer for three international journal namely, Complementary Therapies in Medicine (Elsevier), European Journal of Integrative Medicine (Elsevier), Current Science (Current Science Association & Indian Academy of Sciences).

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FIRST PRIZE (GOLD MEDAL) - 2016

“Clinical Trials in India and China: Advantages and Disadvantages”

Synopsis

In today's global scientific era, clinical trials are the mainstay for bringing newer and better drugs to market and are indispensable part of the drug discovery process to ensure the safety and efficacy of any new drug. Global Pharmaceutical industry is racing for offshore venues to combat escalating Research and Development costs and lengthy clinical trial timelines by outsourcing it to developing countries like China and India. This is mainly because over the past decade of economic liberalization and years of unprecedented growth, these countries have taken significant strides forward as emerging markets in drug development becoming a preferred clinical research destination for MNCs. Rapidly growing pharmaceutical markets and buying power, coupled with the current pharmaceutical annual growth rate of 10–15%, provide further incentive. However, when we compare the recent scenario of clinical research in these two countries, China stands out as one of only a few countries where the number of clinical trials have increased over the last five years. India, on the other hand, is

experiencing a downward trend despite its efforts. Both the countries have their own advantages and disadvantages as a clinical trial destination, however, both India and China are enhancing their efforts to boost the clinical trial industry. Today, world over, a need has been felt on the imperative for transparency, accountability and accessibility in order to re-establish public trust in clinical trial data. Hence, Clinical trial industry in India has great potential to become the most favourable destination in the world. The Government of India needs to create a regulatory environment capable of ensuring the conduct of clinical trials without violation of humanitarian ethics and other social norms. We need to create competencies for clinical trials in the form of better regulation and funding and the training of right human resources so that India can proudly stand among the comity of nations doing clinical trials specifically China.

“Clinical Trials in India and China: Advantages and Disadvantages”

Introduction

Any new drug, treatment device, or treatment regimen that is developed ought to not just be effective for treating the given disease condition but also safe for human use. The **safety** and the **efficacy** of all new treatments is judged through “**clinical trials**”. Since clinical trials are a method of answering unanswered questions regarding new treatments (drugs or devices) or treatment regimen, these are “**research studies**” that are meant to follow strict scientific standards to ensure patient safety and produce reliable study results. In today's global scientific era, clinical trials are the mainstay for bringing newer and better drugs to market and are indispensable part of the drug discovery process to ensure the **safety** and **efficacy** of any new drug.

James Lind is considered as the **father** of clinical trials. From the year **1800** onwards, clinical trials began to proliferate and with the establishment of guidelines for ethical clinical trial conduct and regulations for drug development, more than **1019** novel drug therapies have been approved by the FDA-that's virtually all the medicines used today. Clinical trials hold enormous potential for benefiting patients, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. **There are the following four types of clinical trials:**

Phase 1 Trials: These are carried out in a small group of healthy

volunteers to test for the safe dose for the drug, its side effects, and pharmacokinetics.

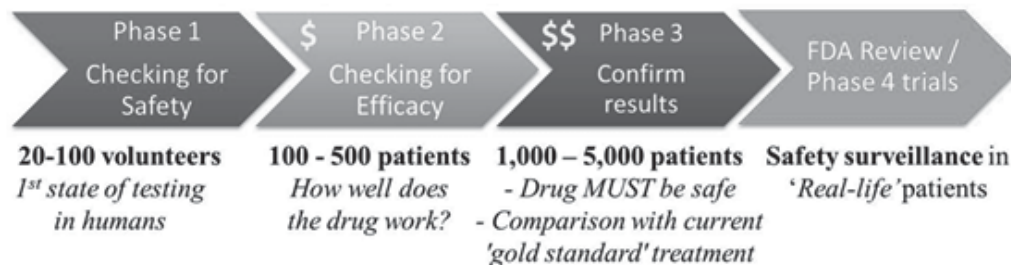


Fig. 1 - Different Phases of Clinical Trial

Phase 2 Trials: They are conducted to test the efficacy of a drug against the specific disease condition, to gather further information on the adverse effects, or to test the dose of maximum efficacy.

Phase 3 Trials: These are much larger trials involving thousands of **patients** and may test a different route of administration, different dose of the standard drug against the standard regimen, or they may test a new drug against the standard treatment for a given condition.

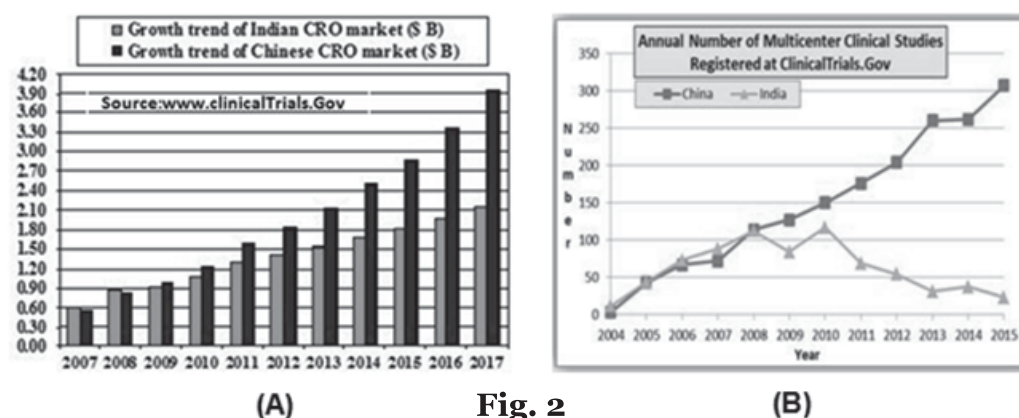
Phase 4 Trials/Post-marketing Trials: These are conducted after it is licensed for a given clinical condition. The usual objectives are to find out long-term **risks or benefits** of the drug or to obtain additional information on its efficacy, side effects and safety.

Clinical trials are of **cardinal importance** in the drug development process and as the western pharmaceutical companies feel pressure to produce innovative, well-differentiated drugs at **reduced costs**, there

has been an increasing trend toward shifting clinical trials to other countries. Estimates predict that nearly **30%** of clinical trials will be conducted in **developing countries** in the near future. In this purview, the large and diverse populations found in **India and China** make them increasingly popular destination for clinical trials.

Paradigm shift in drug development: Focus on clinical research in India and China

India and China together account for 40% of the world's population. Over the past decade of economic liberalization and years of unprecedented growth, these countries have taken significant strides forward as emerging markets in drug development becoming a preferred clinical research destination for MNCs. Rapidly growing pharmaceutical markets and **buying power**, coupled with the current pharmaceutical annual growth rate of **10–15%**, provide further incentive. By all accounts, it appears that most of the major pharmaceutical companies are already conducting clinical studies in these two countries.



Comparative growth of CRO markets and clinical trials in India and China

However, when we compare the recent scenario of clinical research in these two countries, **China** stands out as one of only a few countries where the number of clinical trials have **increased** over the last five years. **India**, on the other hand, is experiencing a **downward trend** despite its efforts. **Fig. 2** describes the comparative growth of CRO markets and ongoing registered multi-center trials in India and China.

Both India and China are striving to **increase the number** of clinical trials. However, they have **challenges** ahead. In the next few sections; we will focus on the **advantages and/or disadvantages** of conducting clinical trials in India and China.

Scenario of Clinical Trials in China

The Chinese biopharmaceutical industry is undergoing a transformation as the government tries to move to an “**innovation-driven economy by 2020**”. China now accounts for almost 18% of worldwide R&D spending across all industries. Healthcare is a particular priority. Since the **Major New Drug Innovation Program (MNDIP)** started in 2009, the Chinese government has strengthened IP rights and made regulations more amenable to innovation as it aims for the discovery of **100 innovative new drugs by 2020**.

Chinese government has put considerable resources behind this objective, investing well over **\$200B US**, creating over **100 life science parks** and over **160 funding programs** to foster drug R&D, and implementing attractive financial incentives for Chinese scientists with western pharma experience to return to China to lead the efforts. As a result, global clinical

trials of innovative drugs have become relatively commonplace in China, driving a steady growth of **23%** CAGR over the last 8 years.

Advantages of conducting Clinical Trials in China

Below discussed are some of the **advantages** for the pharmaceutical companies in conducting clinical trials in China:

- **Revamped Drug Registration Rules (DRR):** In **August 2016**, CFDA's new proposals offer the prospect of eliminating a backlog of drug reviews, updating China's drug classification system and reforming clinical trial rules to allow parallel drug development in and outside of China.
- **Fighting the menace of fraudulent data:** As of **early 2016**, if the CFDA detects falsified data, applicants will not receive approval and will be denied acceptance for at least 1 year. If the trial has already been approved, applicants will face a **fine of \$1,500 to \$4,500** and their clinical trial submissions will be rejected for the next 3 years. Furthermore, the person directly responsible for any error will not be authorized to conduct trials for the next 10 years. **All records of false submissions will be publicized.**
- **Positive Changes in Medical Device Clinical Trials:** In **May 2016**, a new standardized checklist was released by the CFDA to guide medical device clinical trial site inspections. Improvements have been made regarding regulations for handling medical devices during clinical trials:
- **Prioritization of Clinical Trials:** In order to approve more clinical trials, in **August 2015**, the CFDA proposed a new “**four-**

color light strategy” to help prioritize which clinical trials to review first. In this system, proposals would be classified into one of four categories, and then categorized into “channels” according to level of importance.

“Pharmaceuticals attempting to **cure** serious diseases, **such as AIDS and cancer**, are normally **fast tracked** to get clinical trial approval”

- **Marketing Authorization Holder (MAH) system:** On **November 11, 2015**, a new MAH system was introduced in 10 provinces, allowing Chinese manufacturers, R&D institutions, and research personnel to receive approval for their pharmaceuticals even if the products were produced by a CMO.
- **Diseased Population Base:** An ageing population and a rapid rise in chronic diseases including cardio-vascular disease, diabetes, cancer.
- **Sustained Clinical Trial Quality:** The CFDA introduced a list of new items that the clinical trial's sponsor, investigator, and trial site must agree upon in writing, holding all parties accountable to the law while maintaining quality and integrity.
- **Clinical Trial Approval:** New Green Channel and Fast Track paths can potentially speed the approval process.
- **Patient Recruitment:** China typically offers much faster patient recruitment and a larger population of **treatment-naïve** patients. China's clinical trials generally require fewer patients and have shorter duration than the west.

- **Consistent data:** Data produced in China trials can usually be used to support US and European approvals.
- **Sponsorship:** Chinese pharmaceutical companies are often willing to fund the costs of the trials in China in exchange for China rights.
- **Disease Burden:** A high increase in infectious diseases and an extremely densely populated pool of patients. Access to naive patient pools.
- **Healthcare Professionals:** Talent pool of highly trained healthcare professionals who are experienced and motivated investigators.
- **Clinical Trial costs:** Lower costs in comparison to western countries thus overall lower cost of clinical research.
- **GCP Compliance:** High level of GCP compliance at Chinese sites and high quality data.

Notwithstanding all of these positive points, there are a few considerations which should be taken into account by companies conducting clinical research in China:

Disadvantages of Conducting Trials in China:

- **Growing mistrust of Pharmaceutical companies because of falsified data:** Although CFDA has increased penalties for falsified data in clinical trials but as of **early 2016**, there have been **withdrawals from over two-thirds** of the pharmaceutical clinical trial applicants in China. Companies are losing confidence in

continuing their clinical trials in China due to the widespread presence of fraudulent data.

- **Difficulty in doing business:** The country's biggest drawback is the time it takes to authorize a trial there. While it can take up to **4 months in India**, it's rare for a trial to be authorized in **China** in any **less than a year**.
- **Challenging regulatory landscape:** These considerations include a challenging regulatory landscape with changing healthcare policies; import/export requirements; non-compliance to GCP guidelines. As of **late 2015**, the CFDA had only cleared approximately 150 applications from its backlog. Most applications were pulled by the companies themselves, with the CFDA rejecting 13 of the submissions.
- **Increased clinical trial and drug registration fees:** Over the past years, China's clinical trial and drug registration fees have significantly increased. For example, a local product registering in China will cost sponsors approximately 624,000 RMB (~\$100,000 USD), as opposed to paying 35,000 RMB in previous years; **a rise of 1,682%**. Registering a new imported drug has **increased by 2,041%**.
- **Mandatory Submission of self audited clinical Trial Data:** CFDA has mandated submission of self-audit clinical trial data. Failure to submit will **halt the approval process** and those who corrupt data or destroyed evidence will be banned from submitting drug registrations for the following 3 years.

- **Long Approval Timelines:** Indeed, the greatest risk for clinical development in China is the delay in approvals, as the timeframe for a new compound to be approved for clinical trials can be unpredictable. No **30-day** tacit approval for INDs; approval typically issued in **9-18** months.
- **Language Barriers:** Inter- and intra-country language differences may sometimes lead to problems in protocol adherence.
- **Talent war:** There is shortage of well trained and experienced CRA, CPMs, CRC, MW, Stats, along with technical/trial logistics in china.

On the other hand, an attractive destination for conducting clinical trials in recent years is **INDIA**.

Scenario of Clinical Trials in India

India offers rapid completion and reduced cost to the sponsors from Canada, Europe and US. India is working towards “**Pharma Vision 2020**”. The standards to conduct trials have already risen to the International requirements and made India ready to participate in more global trials. India is being presented by a number of companies as the place of choice for the conduct of clinical trials. After India signed **GATT/WTO-TRIPS** agreement, major generic producers were coerced to change their business strategies. Thus, the focus shifted to development of in-house research and development facilities.

Today, several Indian companies are involved in **drug discovery and development**. India, offering huge benefits and favourable conditions to

pharmaceutical MNCs, has made herself an alluring destination for the drug development process. This change has caused the emergence of massive contract research business by CRO's. These CRO's offer a wide variety of services like clinical research, clinical trial monitoring involving several phases, site management, **data operations, discovery sciences, toxicology, pharmacokinetics, genomics, in silico ADME prognosis and even bioinformatics**. MNCs are considering India **advantage** in conducting clinical research here.

Advantages of conducting Clinical Trials in India:

- **Progressive regulatory regime:** Given increasing local demand for clinical trials by a transforming Indian pharmaceutical industry that is looking to develop new molecules and other stakeholders, there is a sense that the regulatory regime will try and help rather than hinder the conduct of clinical trials. Recent regulatory changes have also helped to foster this impression. There has been a marked increase in the number of trials being requested for products that may not be marketed in India. Thus, India as a **preferred location** for clinical trials in general is gaining legitimacy.
- **Patient base and Patient types:** It is a country of over **1.3 Billion** people with a lot of sick people who need treatment. While infectious diseases still dominate the sick population there is an increasing percentage of sick people who have types of illnesses of interest to developed nations. Patients are **multi-racial** and **multi-ethnic** and thus provide a huge genetic variety that is going to be **critical** for testing the next generation of new products.

- **Patient history:** Patients are often “**treatment naïve**”, thus allowing for efficacy tests not possible elsewhere. According to the **DCGI**, India will be a preferred site for clinical trials because, in addition to its medical infrastructure and trained, English speaking human power. It has a diverse population with **6 out of the 7 genetic varieties** of the human race.
- **Patient recruitment and Patient retention:** Subject recruitment is relatively easy and quick due to a high level of trust in the doctors and a trial being at times the only way of getting treatment. Due to the dependency of many subjects on the trial for regular medical treatment and close networks with communities where patients reside, there is a higher retention rate of subjects.
- **Western trained principal investigators:** Most of the principal investigators who conduct these trials have been educated in the West and are familiar with the traditions of conducting trials. State of the art specialty hospitals; in the last few years there have been a number of top-level hospitals with all the required equipment and infrastructure to meet ICH GCP guidelines.
- **Communication and infrastructure:** In the first place, most communication is in English. This is an advantage especially for global trials where India is one of the many sites. India has a very good IT infrastructure making data communications globally easy. India becomes a more obvious choice because this is home to over **16,000 hospitals** and **500,000 doctors**, making it an ideal country, in which to conduct clinical trials.

- **Cost advantage:** Estimates vary but **30%-60%** cost savings in conducting Phase III trials. Subject recruitment costs coupled with high retention rates and costs of salaries of personnel and the overall cost advantage in doing business in India in general are the major sources of savings.

However, the Indian clinical research industry went through a trying phase in 2013 and 2015. There were some significant events that led to the significant decline in number of clinical trials being conducted in India (Fig 1). Important events which led to decline in number of clinical trials in India:

- **April 2010:** 68 Indian human rights and women's groups send a memorandum to the Indian Minister of Health and Family Welfare opposing what they say is the unethical nature of the PATH HPV vaccine trial and calling for it to be halted. In response, the **ICMR suspends the trial.**
- **February 2012:** Indore and Pune based health activist group, Swasthya Adhikar Manch, files Public Interest Litigation seeking justice for “**drug trial victims throughout nation**”.
- **January 2013:** Amendments to the Drugs and Cosmetics Rules specify procedures to analyse the reports of serious adverse events occurring during clinical trials and procedures for payment of compensation in case of trial-related injury or death.
- **March 2013:** The **DCGI** constitutes an expert committee to examine reports of deaths in clinical trials.

- **July 2013:** The **Ranjit Roy Chaudhury panel** established to advise on policy guidelines for approval of new drugs, clinical trials and banning of drugs-publishes a report suggesting major changes, including that clinical trials should be held only at centres that are accredited for the purpose, and that the existing 12 drug advisory committees should be replaced by a single broad expertise-based Technical Review Committee to ensure speedy clearance of applications.
- **July 2013:** The US NIH announces it is **suspending 40 clinical trials in India**.
- **August 2013:** The **DCGI** makes it mandatory for the sponsor or his representatives to furnish the details of the contract between the sponsor and the investigator with regard to financial support, fees, honorarium, and payments in kind to be paid to the investigator.
- **September 2013:** India's Supreme Court suspends all clinical trials of new drugs in the country.
- **September 2013:** Contract research organisation **Quintiles closes** its research centre in Hyderabad, a joint venture with Apollo Hospitals Enterprise.
- **November 2013:** The **DCGI** issues a directive that an audio-visual recording of the process of obtaining written informed consent is required for each trial subject.
- **January 2015:** The health ministry proposes pre-submission meetings in a bid to enable technical deliberations between stakeholders and the drug regulator before clinical trial applications are submitted.

In the past, India conducted a similar number of clinical trials as other developed markets. However, **this trend faced major setbacks because of these events, reducing the number of clinical trials in India by 90% in the last few years.** Companies began to conduct their studies in other countries due to the “**unpredictable and uncertain regulatory environment**” in India.

The global pharmaceutical companies are considering the following India specific challenges as **disadvantages** in conducting clinical trials:-

Disadvantages of Conducting Trials in India

- **Lengthy approval timelines:** International Phase I clinical trials with NCEs developed in a foreign country (first-in-human trials) are not allowed in India. For NCEs developed (or co-developed) in India permission can be granted, but the timelines for approval are approximately 5-8 months. However, **this is still better than China.** Moreover, clinical trials applications submitted to the DCGI where they does not have the competency to review are sometimes referred to outside agencies such as the ICMR, DBT etc for their review and expert opinion, which results in longer review times.
- **Manpower crunch and application backlog:** The DCGI office is facing a serious manpower crunch and this increases the timelines required to review and approve clinical trial applications, which is a hindrance to companies wanting to conduct trials in India.
- **Lack of communication:** As there are no direct communication channels between industry and the DCGI's office, some applications

are queried outright, without the regulator checking the information provided or due to misunderstanding. This puts the application back to the end of the queue.

- **Inadequate Training for Clinical Trials:** Most medical schools lack a formal course in training for clinical research and investigators have relied on mentors to learn how to conduct clinical trials. There is a shortage of trained manpower.
- **Unfavourable Government Policies:** Regulatory approvals in India can take three months or more. Even more serious is the lack of confidentiality. Unlike China, India does not yet grant protection for data gathered from the clinical trials, which makes it easy for generic drug makers to copy the drug data under trials.
- **Weak Patent Laws:** In India, opportunities will become limited unless there are very strong patent laws and mechanisms to enforce them. Drafting patent laws with the help of industry experts and its implementation is highly essential.
- **Implementing GCP:** In India, the experience of conducting global-level GCP-compliant trials is limited. The efforts of the government and industry to create awareness through GCP workshops and to provide training to the investigators will go a long way in creating a culture of global GCP quality trials.
- **Lack of Strong Ethical Committees:** The field is dogged by complaints that Indian trial investigators recruit patient unethically, exaggerate claims and downplay the risks of trial drugs. Institutional ethics committees cannot help much either. In most of the cases, the

committees are headed by the institutional heads. At the federal level, the central ethics committee at the ICMR issues guidelines but has no policing powers.

- **Scientific Misconduct:** Unethical practices, falsified data, fraudulent trial subjects are some the discrepancies. In India exploitation of trial participants are happening because of illiteracy, poverty and unaware of common rights making the poor needy people as experimental guinea pigs. Data integrity has been a major issue in India, with **at least 16 individual Indian manufacturers identified that submitted inaccurate data.** As a result, the U.S. FDA is mandating that some Indian studies be redone.
- **Regulatory concerns:** Although regulations relating to clinical trials have evolved considerably to match global standards, many issues still remain. A major concern is the extreme shortage of regulatory experts. **Unlike FDA and EMEA, DCGI does not release guidance documents.** It is not uncommon to have several experts come to different conclusions about the same regulation.
- **The Deficiencies in the functioning of the ethics committees and CROs:** It has been observed that many CROs in India have an inadequate representation of the non-technical personnel in IEC. Without adequate representation of persons from a non-functional background, the opinion of the IEC is likely to be unfair and biased in favour of the clinical study. Some institutes have IEC but do not have a regular schedule of committee meetings, lack

SOPs or do not have a proper member representation according to the ICMR guidelines.

However, recently there have been spurt of changes introduced by the Government of India, which could serve as revitalize for conducting clinical trials in India. Some of them could be noted as follows:

- **Ease of doing Business:** With the recent initiative by Prime Minister Narendra Modi by introducing “**ease of doing business**” could revitalize the clinical trial industry. Government is offering tax incentive to the CROs. For enhancing the communication between regulatory body and the pharmaceutical industry government has suggested to have discussion before starting the trials. In order to accommodate various religious and cultural practices, patients are no longer required to offer their informed consent through video and audio recordings. India also clarified policies regarding patient compensation during clinical trials.
- **Changes in Drug and Cosmetic Act:** Things are changing fast for the better. New Schedule Y1 is proposed which has mandated registration of CROs and only these registered CROs will be allowed to manage clinical trials. DCGI has been conducting training programs for members of the ethics committees across the country to improve the functioning of IEC. In **June 2016**, India proposed revisions to the Drug and Cosmetics Act of 1940 in order to improve the quality and expedite the process of drug clinical trials.

- **New Rules by DCGI-Steps in the right direction:** In **August 2016**, DCGI eased norms related to pharmaceutical research in India. Under the new ruling, an investigator or researcher can now undertake as many trials as approved by the ethics committee, as opposed to the present cap of 3 trials. The regulator has also relaxed norms for hospitals or clinical sites undertaking such trials. Through a separate notification, the DCGI has **revised the rule** that prohibited any hospital with less than 50 beds to take up a trial.

Conclusions and Way Forward

Emerging economies like **China** and **India** are striving to increase the number of clinical trials being conducted in their respective country. The rises of **China and India** as two key emerging markets provide enormous opportunities to both multinational drug companies and professional outsourcing service providers. In clinical development, **India** currently is a **more ideal** choice than China in terms of the service capability, experience, and CRO choice. However, if considering the factor of the attraction of the local pharmaceutical market, **China** seems to be **more attractive than India** as its current pharmaceutical market is much larger than the Indian market. The incentives for the pharmaceutical industry to conduct trials in these countries include access to large markets, lower costs for the trials, access to large groups of patients with substantial genetic variation and, in some cases, little or no treatment history. Despite all the advantages, both countries are facing the challenge of creating a stable and predictable regulatory environment and developing government agencies that are able to uphold quality in the

application process, implementation and scrutiny of the trials. Above all, the long licensing process is pointed out as being a bottle neck in these countries. In India, but not in China, the confidence of the general public in clinical trials has had a great impact on the formulation and use of regulations. However, low confidence in and mistrust of researchers is the single largest obstacle for the recruitment of trial participants in China.

“Today, world over, a need has been felt on the **imperative for transparency, accountability and accessibility in order to re-establish public trust** in clinical trial data”. Indeed, Clinical trial industry in **India** has **great potential** to become the most favourable destination in the world. The Government of India needs to establish a policy framework for the Indian CT industry to provide for easy access to affordable drugs developed through adaptive clinical trials in India. There is also a need to create a regulatory environment capable of ensuring the conduct of clinical trials without violation of humanitarian ethics and other social norms. To favour the **promotion** of clinical trial in India, restrictions are necessary to ensure **safety** of the trial subjects providing adequate health insurance and compensations. CDSCO has taken noteworthy step by launching online CTRI ensuring accountability, transparency and information sharing on clinical trials making it a public domain. We need to create **competencies for clinical trials** in the form of better regulation and funding and the training of right human resources so that **India** can proudly stand among the comity of nations doing clinical trials specifically China.



SECOND PRIZE (SILVER MEDAL) - 2016

“Clinical Trials in India and China: Advantages and Disadvantages”

Synopsis

India is considered as a preferred site for conducting global clinical trials. Existence of a large treatment-naïve population, availability of English-speaking, skilled doctors, plenty of clinical material, and cost-savings are obvious advantages for carrying out clinical research in India. However, challenges exist at various levels. Lack of formal training in bioethics and research methodology, heavy burden of clinical duties and sub-optimal administrative support restrict investigators. Absence of oversight of functioning of ethics committees (ECs) and lack of mechanisms for ensuring quality of ethics review heighten societal concerns about safety of participants.

China too has experienced a high number of clinical trial applications, which rose from 14,235 in 2013, to 18,597 by the end of 2014. The incentives for the pharmaceutical industry to conduct trials in this country include access to large markets, lower costs for the trials, access to large groups of patients with substantial genetic variation and in some cases, little or no treatment history. Also its highly sophisticated infrastructure and highly trained personnel make it an ideal location for clinical trials globally. This country too, is facing the challenge of creating a reliable regulatory environment and developing government agencies that are able to uphold quality in the application process implementation and scrutiny of the trials.

“Clinical Trials in India and China: Advantages and Disadvantages”

Clinical trials are the gold standard in the field of evidence based medicine. Improvement in therapeutic regimens and advances in medical practice are based on results of clinical trials. Thus results of the clinical trials are useful for the benefit of patients and advances in clinical medicine.

Clinical trials are the scientific term used for testing of newly evaluated drug and to know the safety and efficacy of that new drug. The clinical trials are conducted to know the safety and effectiveness of the new drug and to know the clinical use the drug with the involving of the human subjects. Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutics intervention on patient must be approved by a supervening ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise non interventional studies.

For a few decades now, the Western countries have created a niche for themselves in terms of clinical research. However, since the last few decades, Asian countries have emerged as hubs for conducting major global multinational clinical trials. Two major countries, ripe with potential are India and China. They have an

edge over the Western countries in terms of certain aspects of global clinical trials.

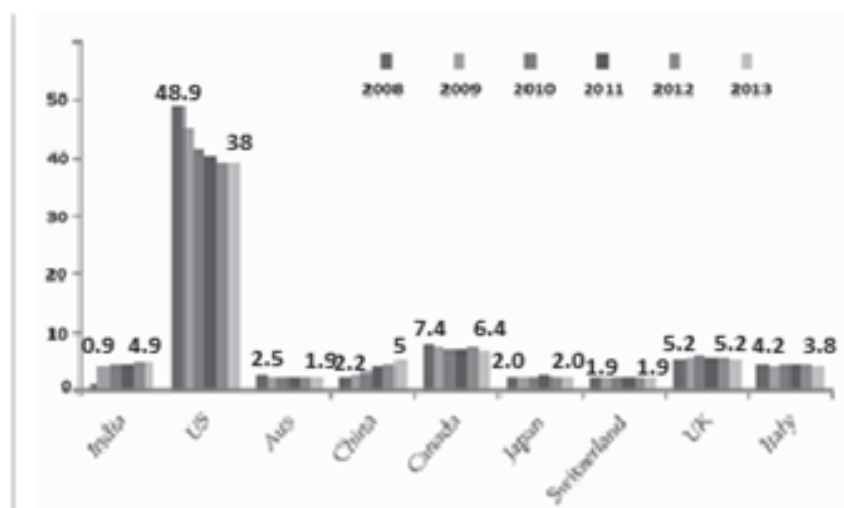


Figure 1: Global share of clinical trials by the country

INDIA A NEW HUB FOR GLOBAL CLINICAL TRIALS

Major Pharmacy companies to look at alternative destinations for sourcing patients for their global studies. Exploration on these lines guides pharmacy industry to take interest in the countries like Latin America Eastern Europe and Asia. In Asian countries, India has the potential to establish itself as a hub for global Clinical Trials (CTs). There are several reasons to it, including but not limited to – a large treatment naïve population with diversity in the gene pool with a range of illnesses, many easily accessible tertiary care hospitals, relatively lower cost of clinical trials compared to the western countries, high enrolment rates, good patient compliance/retention, ICH GCP trained healthcare professionals (HCPs), a generation of gifted young medical students, scientists and researchers who are eager to contribute valuably to the advancement of

medical science, availability of trained man power and infrastructure and fairly accommodative regulatory environment at least until now.

However, the current scenario tells us a different story. The recent amendments to regulation, has contributed to a decline in the Indian Clinical Trial Industry. There are several challenges that the sponsor companies are facing due to uncertain regulatory environment here.

The Indian Advantage

Patient availability: According to their estimates, India stood second (after China) in terms of patient pool for CTs. India provides an excellent diversity in patient population and has a rather large patient base. Also, patients are multi-racial and multi-ethnic and thus provide a huge genetic variety that is going to be critical for testing the next generation of new products.

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.

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 diseases. There is a bulk of patients who are willing to participate in clinical

trials in India for common diseases as well as fatal diseases like cancer, AIDS and other lifestyle diseases of interest to developed countries.

Trained Personnel : Highly skilled manpower is needed to conduct clinical trials and is the most crucial factor while carrying out a clinical trial. India comes at the first place in terms of education and trained doctors when compared with US and China. Moreover, doctors are well trained as per CDSO/GCP guidelines too. US equals India in terms of education and qualified doctors, but the points for skilled labor still goes in the favor of India

State of the art specialty hospitals : In the last few years there have been a number of top-level hospitals with all the required equipment and infrastructure to meet ICH GCP guidelines. At present, India can offer a considerably good and suitable infrastructure for conducting clinical trials. Tata Memorial Hospital in Mumbai, India, is an example of a specialty oncology center that is very well suited to participate in global clinical development. Each year 25,000 cancer patients visit this hospital, not only from India but also from neighboring countries

Communications infrastructure: In the first place, most communication is in English. This is an advantage especially for global trials where India is one of the many sites. India has a very good IT infrastructure making data communications globally easy. Moreover in China, the common language spoken is Chinese, not English and thus makes it a big disadvantage for China.

Cost advantage : Certainly the economic advantages of conducting trials in India cannot be denied. Cost savings in clinical trials could be substantial, resulting from a combination of the different factors. Estimates vary but 30%-60% cost savings in conducting Phase III trials are mentioned. Subject recruitment costs coupled with high retention rates and costs of salaries of personnel and the overall cost advantage in doing business in India in general are the major sources of savings. The shortened timeline due to quicker subject recruitment is a major factor in providing cost savings.

A 2004 study by Rabo India Finance found that phase I trials in India cost less than half of similar trials in the United States; Phase II and III trials cost less than 60% of their American equivalents.

Progressive regulatory regime : Recent regulatory changes have also helped to foster this impression. Since January 2005, concurrent global trials have been allowed in India for Phase II and Phase III. Phase I trials for molecules not discovered in India are discouraged, although case-by-case exceptions can be made based on therapeutic urgency to the Indian population. A number of companies have found these arguments persuasive. There has been a marked increase in the number of trials being requested for products that may not be marketed in India.

The new rules drawn up by the government as of 2013 has returned India to global standards and this should open up more opportunities to do trials here. Also, Improved regulatory environment such as the notification of

amended Schedule Y, publication of revised national guidelines for biomedical research, changes in rules doing away with “phase lag” in clinical trials and introduction of a new patent regime in pharmaceuticals respecting product patents (instead of just process patents).

Indian Scenario Challenges

Ethical issues : Even though, India has the manpower, experienced HCPs and infrastructure to handle more CTs, ethical oversight is somewhat missing. International companies are losing trust in the Indian institutes, as there have been cases of unethical practices in the past. Until very recently, the ECs were not required to register with the DCGI. This led to independent working of the ECs leading to in few cases frauds and manipulation of trial data.

Another important challenge lies with the protection of rights of the subjects in the CTs. No transparency in informed consent processing, until quite recently. Although as of 2013, regulatory authorities have made it mandatory to obtain audio-visual recording of the consent.

Recently Supreme Court of India has criticized the government severely for being lax about CT deaths and unauthorized trials and banned new molecular entity trials under certain conditions (Times of India January 3, 2013). The apex court further instructed that the government come up with a new regulatory regime for CTs that reflects the concerns of all stakeholders, including those who volunteer to undergo the tests at the risk of adverse health effects and even death.

Quality Issues : GCP issues, documentation issues, data quality/data protection/data compromise and fraud issues are predominant in the Indian context. Issue of quality and documentation need to be addressed thoroughly. In recent inspections by US-Food and Drug Administration, it was found that Indian sites could have built in better quality in their trials had they been paying more attention to some particular areas. For example, protocol non-compliance, inadequate or inaccurate records, inadequate drug accountability, informed consent issues and adverse event reporting are the most common quality lapses our CTs. When it comes to documentation in general, Indian sites understand the value and practice of a thorough and compliant process.

Regulatory issues : Clinical trials are regulated per Schedule Y of the DCR. The DCGI is equivalent to the commissioner of FDA, and Schedule Y is equivalent to the IND regulations described in 21CFR.

Unlike in the US, where a sponsor can proceed with a clinical trial 30 days after submission of an IND application if FDA has not commented, in India, the sponsor or its agent in India must receive written approval from the DCGI to proceed with a clinical trial. The review of a clinical trial application could take up to six months, or even longer if the DCGI has queries about certain aspects of the study.

The 59th report of Parliamentary Standing Committee on Health and Family Welfare stated gross lack of qualified staff, lack of co-ordination between various agencies, improperly conducted trials for 39 drugs and 33

new drugs approved without conducting clinical trials on Indian patients in the period of January, 2008 to October, 2010. This report opened the eyes of the regulatory bodies and various amendments are applied to make conduct of clinical trials more stringent, reliable and transparent in India.

CHINA EMERGING HUB OF GLOBAL CLINICAL TRIALS

As a highly attractive clinical trial destination, China continues to see an increased interest from CROs, pharmaceutical companies, and biotechnology firms. With a growing demand for modern pharmaceuticals, China has built a well-established tradition of developing medicines from basic research over the years. In 2015, China conducted 722 clinical trials, with this number expected to increase each year. Similarly, China's registered interventional studies have increased almost 90% between 2008 and 2013.

Recently, the China Food and Drug Administration (CFDA) has issued a raft of new regulations and policies that aims to develop a more scientific and efficient process that would ensure the safety and quality of medicines available on the Chinese market. While a step forward in the increasing sophistication and maturity of the Chinese healthcare market, these changes increase the cost and complexity of entering the lucrative market.

The Chinese Advantage

Patient density: Perhaps the biggest advantage that developing countries like India and China have is that they have a huge population, which ensures higher amount of patients to be enrolled for clinical trials. A high increase in infectious diseases and chronic diseases including cardio-

vascular disease, diabetes, cancer has been observed over the years which adds to the patient pool.

Infrastructure and technical expertise: A talent pool of highly trained healthcare professionals are also ever present in this country and thus add to the benefit of the CRO's. The infrastructure is highly advanced and is almost at par with the western countries. Also the equipment and infrastructure meet ICH guideline, which makes this country highly lucrative for the western countries to invest in.

It's the economic downturn time and now I think it's become a very essential time for improving cost-effective areas. That's why a lot of global companies are now setting up specifically for their outsourcing resource in China instead of outsourcing offices across China, to help develop the program. By doing that, they cut the cost significantly. In general, the conduct of clinical trials is about half of the cost compared to US.

Technological advancement : The biggest opportunity is that now China has set “innovation-driven development” as a national policy for development to encourage more sectors to be innovative. China has increased investments in R&D by about 20 percent every year in the last decade.

We're even seeing new policies issued by China FDA to regulate drug development. We're starting to see strict regulations that need to be enforced for the whole industry, including academic hospitals participating in clinical development to conduct high quality research.

Regulatory reforms : Traditionally, the approval timeline for Clinical Trial Applications (CTAs) has limited China's participation in global trials. However, the time has been reduced to an average of 7 months for NCEs and 12 months for biologics—a notable feat considering that the number of approvals has also been increasing by 18-20 percent over the past two years. (Approval time could potentially be improved still more if China were to differentiate the data requirements and review process for CTAs from that of New Drug Applications (NDA)). The CDE has recently reorganized with the goal of optimizing its review efficiency. The agency has also issued guidelines (CDE Good Practice Review and CDE Drug Scientific Review Decision Path Practice) to improve its practices.

Chinese context Challenges

One of the biggest challenges faced by China in context of clinical trials is that the regulatory bodies, namely CFDA has set up very stringent preclinical requirements. These requirements are relatively much more rigorous than those set up by the Western countries (e.g., two species, six-month toxicity studies data). This makes it very difficult for the CRO's to obtain clearance since a lot more cost is exerted in setting up the standards to the mark prescribed by the regulatory bodies.

Another such policy involves the no 30-day tacit approval for INDs which is generally prescribed by the regulatory bodies globally. Here the approval is typically issued in 9-18 months, prolonging the time frame for the approval of a single molecule. This makes the entire process highly laborious and time consuming. In the west, the development of a new chemical entity

(NCE) drug usually spans a decade or more. Similarly, the approval process for a drug in China also requires a lengthy journey to fulfill all the preclinical and clinical regulatory requirements.

A CFDA regulatory requirement states that clinical trials can be conducted only at CFDA approved clinical sites. This limits the options for clinical trials to be conducted since setting up these sites is a lengthy and expensive procedure. Also, the status of applications are not as transparent as they are in the West. For example there is no publication of results and often there is a silent rejection. This demotivates the local companies to invest in clinical trials on a large scale

The biggest challenge in clinical research in China is finding high quality human resources for high quality clinical research. The education system is designed to train physicians to provide medical service, but there's not enough training on how to do discovery and research. Clinicians are experienced in clinical practice and they understand the disease because of their training, but they haven't received the same level of training to conduct high quality clinical studies. Also the primary language is a major barrier in China since all the communication and documentation is mainly done in Mandarin, as opposed to the globally prescribed English language.

There's not enough money in research funding allocated exclusively to support clinical research. In the past, China was too poor to invest in research, but now with improvements in statistics and epidemiology and other methodology disciplines in China, there is a realization that clinical

research is very important and is an area we should increase investment. But still there is not enough research funding being allocated to clinical research, and that needs to change. Also there is a lack platforms in China, particularly in the academic institutions, to conduct clinical studies.

Conclusion

The last 10 years have been witness to an increasing number of clinical trials conducted in India and China. The result has been anexponential growth in the number of clinical trials conducted in these countries. 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.

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. 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.

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. The technological advancement and funds available for research and clinical trials are better

in China than in India. Also their infrastructure and quality is at par with the Western countries, which makes it highly efficient and reliable.

The road is ofcourse a bumpy one but the recent regulatory amendments call for a fresh breath of air in the clinical research industry gripped by ethical issues and non transparency. Both the stringent procedure for clinical trial approval and patient recruitment has had a severe impact on the industry in the past few years. All that can be expected in the coming few years are more refinements to cover the loopholes in the regulations to make India and China, a trial and patient friendly global destination.

In the last few years, several large pharmaceutical, biotech and medical device companies like Aventis, Merck, Wyeth, Bristol-Myers Squibb, Roche, etc. have outsourced the majority of their discovery and preclinical work to China and India to contain costs and reduce financial risk. Increased globalization of preclinical studies is expected to become the norm in the near future, leading to more successful drug development projects.



SECOND PRIZE (SILVER MEDAL) - 2016

“Clinical Trials in India and China: Advantages and Disadvantages”

Synopsis

World Health Organisation defines a clinical trial(s) (CT) is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. CT hold enormous potential for benefiting patients, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. CTs are either, explanatory or pragmatic trials. There are mainly 4 phases of CT, namely Phase-I to IV, depending objectives and sample size of CT. Depending on study design, CT may also be classified as, retrospective/prospective, parallel/cross-over, open/blinded, randomized/otherwise, placebo/standard controlled.

Ideally, CT should be conducted throughout the world, so that the innovation made can equally be beneficial for humanly use. But, this is not case due to many reasons, which includes but may not be limited to, regulatory measures, governing bodies and their healthy, effective/rapid

involvement, cost, availability and quality/educational status of all the stakeholder of CT, socio-religious and ethico-legal factors, and data integrity, etc. Depending on these confounding factors sponsor/innovator favors one country over the other. India and China were assumed to be ideal place for CT. But due to many reasons they both loosing and/or trying hard to regain the status of ideal place to conduct CT. Here, we have focused on how India and China are transforming in this journey and how they further need to groom themselves. A good CT simply wouldn't be possible without complete, active, ethical, moral and legal involvement of its all the key players. *Both India and China have to continuously focus on how they can increase the CT's quantity, quality, safety and GCPs in their respective countries. At every juncture related to CT, India and China are on a journey of double edge. A simple ignorance or carelessness either way may harm their probable ideal status to conduct CT irreparably.*

“Clinical Trials in India and China: Advantages and Disadvantages”

(A) Introduction

World Health Organisation (WHO) defines a clinical trial(s) (CT) is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. CT hold enormous potential for benefiting patients, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. CT are either, (i) Explanatory trials (sometimes referred to as 'Phase-0 trials' or 'pilot studies') seeking to determine whether a treatment is efficacious or (ii) Pragmatic trials investigate effectiveness– whether it works in real world practice conditions. There are mainly 4 phases of CT, namely Phase-I to IV. Phase-I CT are done in healthy subjects (unlike phase-II, III, IV) to test a new biomedical intervention for the first time in a small group of people (e.g. 20-100) to evaluate safety, pharmacokinetics and pharmacological effects. This data can permit the design of well-controlled, scientifically valid, Phase-II studies. Phase-II CT are done in several hundreds (e.g. 100-300) participants to determine efficacy and to further evaluate its safety. Phase-III CT are done to study the efficacy and adverse effects of an intervention in large groups of trial participants (e.g. 1000-2000) by comparing the intervention to other standard/experimental interventions (or to non-interventional standard care). While, Phase-IV (postmarketing surveillance) CT are done after an intervention has been marketed. These studies are designed to monitor the effectiveness of the

approved intervention in the general population and to collect information about any adverse effects, drug-food-interactions associated with widespread use over longer periods of time. Depending on study design they may also be classified as, retrospective or prospective, parallel or cross-over, open or blinded, randomized or otherwise, placebo or standard controlled.

Ideally, CT should be conducted throughout the world, so that the innovation made can equally be beneficial for humanly use. But, this is not case due to many reasons, which includes but may not be limited to, cost of CT, regulatory measures, governing bodies and their effective/rapid involvement, availability and quality/educational status of all the stakeholder of CT, socio-religious factors, ethico-legal factors, overall quality of CT and its data integrity, etc. Depending on these confounding factors sponsor and/or innovator favors one country over the other. India and China were assumed to be ideal place for CT. But due to many reasons they both loosing and/or trying hard to regain the status of ideal place to conduct CT. Here, we have focused on how India and China are transforming themselves in this journey and how they further need to groom themselves.

(B) Key players of CT

A good CT simply wouldn't be possible without complete, active, ethical, moral and legal involvement of its all the key players. Both India and China are highly populated countries with very large and sufficient sample size and required infrastructures for any kind of CT.

But, there are pros and cons and/or limitations-n-drawbacks of both the places with one and another key player(s).

- (1) **Subjects or legal guardians:** Both India and China are developing countries with many common problems like, poverty, lack of education, health awareness, etc. In both India and China, recruitment of patient is not done in ideal way. Legal guardians are required for vulnerable population. There are many cases has been reported that recruitment of a subjects is highly affected by educational and socio-economical status. Informed consent form (ICF) is not taken properly, either subjects are not well informed and/or subjects are money driven. But, now a day's government of both country taking serious actions. For the same, in India audio-visual ICF has been implemented. This has helped in reducing the malpractices.

India/China both are more suitable place to conduct the CTs of drugs with narrow therapeutic window, higher plasma protein binding, sensitive to individualization (especially concerning to polymorphic drug metabolizing enzymes and/or transporters), etc. Comparing to these confounding factors India provides more homogeneous to heterogeneous population than China, due to number of religions, different socio-economic strata's, highly variable and different environmental and geographical status of the country.

- (2) **Regulator:** Process and review CT applications in accordance with the regulations. Conduct inspections of CTs. Issue the decision

(authorization/rejection). Implement regulations, guidelines, systems and procedures to:

- Protect CT subjects
- Ensure scientific research has merit
- Ensure consistency in the assessment of CTs
- Maintain sponsor, stakeholder, and public trust

To increase transparency, accountability and accessibility in order to re-establish stakeholders trust in CT data. This would be feasible only if all CT conducted are registered in a centralized CT registry. Indian government has made compulsory to register every CT on government registry (CTRI) and to timely update the same. China provides data updates every week to WHO's International CT Registry Platform whereas India updates every 4 week.

- (3) **Sponsor:** Submit an application for authorization of a CT in accordance with the regulations and guidelines. From the sponsor's eye India is better place to conduct CT than China because of better and easy availability of English speaking, highly skilled and trained doctors and other stakeholders of CT.
- (4) **Institution:** Conduct the CT in accordance with the applicable regulations and Good Clinical Practices (GCPs). The Contract research organizations (CRO) and/or institutions following GCPs are increasing in past few years in India compared to china.
- (5) **Institutional Review Board (IRB or IEC):** It's a committee that

has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans. They often conduct some form of risk-benefit analysis in an attempt to determine whether or not research should be done. The purpose of the IRB is to assure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in a research study.

The Ministry of Health's National Biomedical Research Ethics Committee manages and oversees all biomedical research ethics in China. The interaction of the local ECs with the national committee is for professional guidance. Most of the ECs existing in China are hospital ECs which have developed over a period of 10 years. IECs also exist in China. They have been established in compliance with World Health Organization (WHO), United Nations Educational, Scientific and Cultural Organization, and GCP guidelines. While, in India CDSCO has undertaken the process of registering IECs in 2013. It is now mandatory to seek approval from an IEC which is registered with CDSCO, before starting any CT in India. This is a milestone in the evolution of clinical research (CR) in the country. More than 500 ECs have been registered as of today. The IECs have received approval from CDSCO to evaluate bioavailability-bioequivalence (BA-BE) studies only. The institutional ECs have received approval to review CT. The registration has been issued for a period of 3 years, after which the committees need to reapply.

(6) Principal investigator (PI): Person who leads the research team

running the trial. They're usually a specialist doctor and/or researcher. It has been found that PIs of CAM are less serious and/or updated compare to Allopathic/modern PIs. This increases chances of noncompliance, misconduct, and/or fraud with increasing intensity of malpractice. (Figure-1)

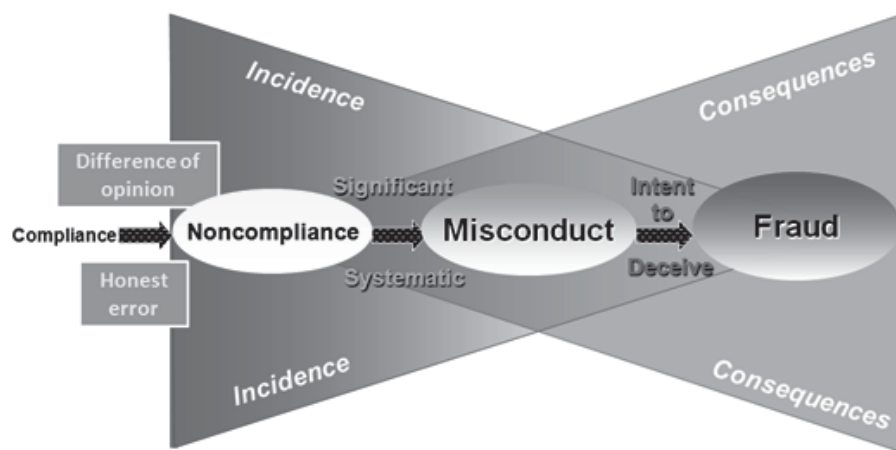


Figure-1 Sequence and impact of malpractices during clinical trials

(A) CTs in India and China:

Both India and China has long back history of well developed medical practices, which can't be developed without some evidence based research-a kind of CTs. Ayurveda is 5000 BC old, while traditional Chinese system of medicine is over 2,500 years of Chinese medical practices. 2015 data reported that, 1.4% of global CT are currently carried out in India compared with 3.2% in China, 1.5% in the Czech Republic, 1.0% in Turkey, and 0.9% in Thailand. Half of all trials being conducted worldwide are based in North America, with the UK hosting 5.5% of trials. Considering the current scenario, both India and China despite of having sufficient resources to carryout CTs they has long way to become ideal place to conduct CT.

- (1) **China Pharmaceutical CTs:** In order to approve more CT proposals in a timely manner, the China Food and Drug Administration (CFDA) has gradually updated the pharmaceutical CT regulations. In August 2015, the CFDA proposed a new “four-color light strategy” to help prioritize which CT to review first. In this system, proposals would be classified into one of four categories, and then categorized into “channels” according to level of importance. Pharmaceuticals attempting to cure serious diseases, such as AIDS and cancer, are normally fast tracked to get CT approval. On November 11, 2015, the CFDA published a review detailing four new initiatives. A new Marketing Authorization Holder (MAH) system was introduced in ten provinces, allowing Chinese manufacturers, R&D institutions, and research personnel to receive approval for their pharmaceuticals even if the products were produced by a contract manufacturing organization (CMO). CFDA also modified various definitions in the Chinese pharmaceutical field, including “novel drugs” which are now limited to drugs that have never been approved and marketed anywhere in the world. The CFDA has also increased penalties for falsified data in CT. As of early 2016, there have been withdrawals from over two-thirds of the pharmaceutical CT applicants in China, a rate that is still increasing. Companies are losing confidence in continuing their CT in China due to the widespread presence of fraudulent data. Now, if the CFDA detects falsified data, applicants will not receive approval and will be denied acceptance for at least one year. If the trial has already been approved, applicants will face a fine of \$1,500 to \$4,500 and their CT submissions will be rejected for the next three years. Furthermore, the person directly responsible for any error will not be authorized to conduct trials for the next ten years. All records false submissions will be publicized. **But it seems that, these all efforts are baseless, as despite of these acts/laws, Oct 2016 report**

shows that, almost 80% of data of all ongoing Chinese CT have been fabricated.

- (2) **India Pharmaceutical CT:** In the past, India conducted a similar number of CT as other developed markets. However, this trend faced major setbacks in 2015, reducing the number of CT in India by 90% in the last few years. Companies began to conduct their studies in other countries due to the “unpredictable and uncertain regulatory environment” in India. Data integrity has been a major issue in India, with at least 16 individual Indian manufacturers identified that submitted inaccurate data. As a result, the USFDA is mandating that some Indian studies be redone. In recent years, India announced new reform policies for the CT process. First, in order to accommodate various religious and cultural practices, ICF through audio-video recordings is mandated for vulnerable population and on case to case basis. New IEC requirements have also been established, such as having to register with the Indian Licensing Authority before starting a CT. Foreign CT data is generally accepted, as long as the foreign CT inspection certifies the data complies with GCP and the Code of Federal Regulations. Rather than conduct a full CT in India, some companies may do an Indian bioequivalence study instead, abiding to BA-BE guidelines-2005, and the checklist for pre-screening applications-2014. In about 50% of the cases, foreign companies can apply to waive the BE study. If a branded drug was approved in India four or more years ago, the bioequivalent drug may be approved without any local studies in India. In June 2016, India proposed revisions to the Drug and Cosmetics Act of 1940 in order to improve the quality and expedite the process of drug CT. India asked U.S. and European regulators for their opinions, which will hopefully be drafted by the end of 2016.

(3) Government/Regulators:

It is important to note that CT in India have a political context that is mostly absent in other countries. Given the uncertain regime, drug companies and CROs are cutting back on CT in India. *The hub appears to have shifted to China, where a lot of government support has come to the aid of the industry. in terms of easier processes, lot of government support has come to the aid of the industry.* CFDA has recently released draft guidance on data integrity in clinical research. English has also been made mandatory in China, which has given a fillip to most CROs to take on work from multinationals.” This made easier to conduct business outside India. But, from 2010–2011, things have changed quite drastically for CROs. Eastern Europe used to charge heavily, so many of the multinational companies moved to India, where it was 40% cheaper to conduct trials and there is a ready demographic. Despite government of India has announced that it will sell its CR business, the companies still finds the regulatory challenges that have made it difficult to scale up the business. On the other hand some of Indian pharmaceutical companies, such as Biocon, Alembic, Zydus Cadila, Torrent and Lupin, have already moved trials out of the country. At Biocon, the research and development (R&D) spend is 134% higher in the second quarter of 2015 compared with 2014.

In Aug 2016 Indian government has updated the guidelines, (a) As regards restriction that no PI shall conduct more than three trials at any given period of time, it has been decided to remove the restriction and it is further decided that IEC after examining the risk and complexity involved in the trial being conducted/proposed shall decide about how many trials an investigator can undertake. (b) As regards condition that no CT shall be conducted at site having less than 50 bedded hospitals, it has been decided to revise this

condition and it is further decided that IEC shall examine and decide whether the CT site is suitable for trial or not irrespective of number of bed. (c) The Drug Controller General of India (DCGI) has ordered companies to self-assess their compliance with good manufacturing and laboratory practices (GMPs/GLPs). DCGI is demanding to award themselves quality rating and submit the resulting report to the relevant regulatory officials. DCGI's decision to place the burden for making these assessments onto manufacturers is reminiscent of the strategy pursued by CFDA. CFDA claims the approach has delivered some success, notably in terms of shortening its backlog of regulatory submissions. (d) *Requirement of approval of Review Committee on Genetic Manipulation (RCGM) under Department of Biotechnology for r-DNA derived drugs:* The applicant may submit parallel applications to the RCGM and DCGI seeking approval to conduct CT involving r-DNA derived drugs. DCGI will complete the review of the application and issue permission, only after RCGM clearance is received. With these new requirements in place, processes such as assigning new sites/investigators to a study; facilitating the conduct of out-patient based studies at small hospitals/clinics that have larger patient pools; allowing motivated, research-focused investigators to undertake more trials at appropriate sites and, *potentially reducing CT approval timelines for rDNA based products*, will help to streamline CT set up and ongoing operations for sponsors. Apart from such modifications Indian government need to take very serious steps to improve the India's CR sector. *Current, PM of India, Mr. Narendra Modi's vision and his way of working has changed views of entire world to look at India, since he himself treats his government as a startup. Government support has increased drastically. Recently India passed GST bill which going reform entire country's taxation system to one country one tax system, which will help global CRO, CMO to significant*

level. Considering these reforms and their rate of change/update in Indian government and regulatory bodies working pattern/strategies India holds very strong potential than any other country to become ideal place to conduct CT and/or CR related business.

- (4) **IRB or IEC:** Accepting the fact that, both India and China are developing countries, they face many problems/limitations. One of them is all hospitals may not have the financial and operational capabilities to form and operate an IEC; they shall have the option of approaching a registered IEC from their locality for review of their research documents. But all IECs may not be well equipped to handle outside projects, and the individual clinician researcher may not be able to pursue research due to lack of access to IEC. Also, although ECs are responsible for ongoing review and monitoring of trial activities; due to lack of space, infrastructure, time, funds, and administrative support; most IECs restrict themselves to an initial review and approval of study protocol. Therefore, government needs to take initiative to form a network/cluster of IECs to solve such problems.

Apart from documentation/legalities, there is need to understand and take necessary actions against those bypassing the rules/regulations. For instance, Wang's IRB is one of the best regarded IRB in China. According to Wang's IRB, "if we reject sponsor with no/incomplete ICF, they often just go somewhere else". So there should be strict action against such illegal, immoral, unethical actions.

- (5) **Compensation:** Ensuring uniformity and fairness in compensation payments in a trial is another challenge faced by the IECs. It would be best if

the assessment of causality and the method for calculating the quantum of compensation determined upfront and IEC confirmation taken before the start of the study. But there are no definitive guidelines available to aid the IEC to ensure that the patient is rightly compensated.

An ideal solution would be the formation of national and regional ethics committees under the wings of CDSCO (India) or CFDA (China). These committees could play a supervisory role in guiding the IECs and also review documents for independent researchers. This would serve to make the existing IECs uniform and resourceful and may pave way to the harmonization of the IEC review process, which would benefit the research industry as a whole.

There are more reports associated with issues in compensation in China compare to India.

- (6) **Awareness among doctoral researcher's:** Doctoral research scholars (MD, MS, and PhD) who dose CTs for their research/thesis work that should be done ethically and morally. It has been observed that there are no strict and/or stringent rules and regulations in both Indian/China, which in majority of cases leads to journey of CT from non-compliance to misconduct to generation fraudulent data. This is also risky for patients who have been taken as subjects in medical colleges. Therefore GCPs should be strictly followed and strict actions should be taken regulators against those who don't follow GCPs. These kinds of problems are higher in the colleges those in remote/underdeveloped area or with less patients load. Such early level of ethico-legal and moral practicing habit can reduce the patients suffering, as these researchers are future PIs.

- (7) **Role of media and Community awareness:** Media holds strong potential to alter the views of all the stakeholders of CT and among them, subjects/patients are the most vulnerable. Recently in India, NGO-Bill gates foundation has been involved in misconduct-fraud in vaccine trial, where they used Indians as guinea pigs. *But media sometimes unnecessarily use this word “guinea pig” and create fear in the mind of subjects.* It is worth to note that, the importance of drug trials in promoting health cannot be overemphasized. New drugs had a tremendous impact on the life of patients. It is essential to continue with drug trials more vigorously than before, the more so in a country such as India and China. In the past, when the patent regime did not favour the discovery of new drugs, India/China had to depend on drugs developed abroad. As more subject-friendly rules are made, we should try to maintain a balance so that India/China remains an attractive destination for the outsourcing of CT. An excessive increase in the cost of the trials will eventually affect the cost of the new drugs. Let us remember that it is finally the patient who pays for it all.
- (8) **Medical Devices:** There have been important updates to the regulations governing CT in several of the Asian countries in recent years. *In December 2015, the **China's CFDA** added 114 Class II and 8 Class III medical devices to the CT exemption list.* In May 2016, a new standardized checklist was released by the CFDA to guide medical device CT site inspections. In June 2016, changes to the New Device GCP guidelines went into effect. If the sponsor is located overseas, the company must assign a local China agent to oversee the China CT. Furthermore, the sponsor has been assigned additional responsibilities, including appointing qualified supervisors, additional PI (multicenter CT), revising investigative brochures, and getting necessary approval from IEC. Improvements have been made regarding

regulations for handling medical devices during CT:

- The sponsor must label fully tested devices as “investigational devices”.
- Devices are only given to relevant people.
- “Investigational devices” are disposed of properly based on previous agreements.

The CFDA introduced a list of new items that the CT sponsor, investigator, and trial site must agree upon in writing, holding all parties accountable to the law while maintaining quality and integrity. The CFDA defined “multicenter study” as a study that takes place at three or more sites following the same protocol.

In **India**, medical device approval generally does not require local CT, since foreign data can often be used. CTs in India are typically only required for risky medical devices without predicates.

(9) Ayurvedic or Chinese CAM drugs/formulations CT and issues

Procedure of planning, development, evaluation, regulation, management and approval of CTs of CAM need to be done with special considerations, as they involve multiple factors as treatment measures and now days the CAM practitioners prefer “**Black box designed CTs**”. There are no internationally harmonized guidelines for the same. *IRB/IEC needs to be trained with additional experts from integrative-personalized medicine, respective CAM. When discussing **issues** about misleading verses counterfeit medicines*, issues with CAM drugs comes on top of the list. Both India-China has these issues with varying intensities. Without proper CTs new CAM drugs get very easy marketing approvals. For instance, in India, even central research institutes like, CCRAS, CDRI, NRDC, CSIR are making

very big claims lacking sufficient scientific evidences, and selling their CAM drugs with misleading advertisements. It is hoped that the new Consumer Protection Act 2015 Bill (India) and the law will take strict actions.

Every one or other day USFDA publishes reports about counterfeit warning for CAM drugs (mainly Chinese), these drugs get approval based CAM/TCM/Ayurveda claims and/or fraudulent CTs. Hence, internationally harmonized laws need to develop to address these issues.

Future perspective:

(1) Policies concerning to novel developments:

AyurOmics: Ayurveda understand the individualization in classical manner with the help of “*Prakriti*” concept. Concept of AyurOmics came from AyuGenomics, which has been formed by blending of Ayurveda and Genomics, which holds strong potential to overcome all major hurdles of current omics based approaches. Therefore, this novel approach may have potential to bypass the need of a *Multi-regional CT*. As “*Prakriti*” concept focuses on all the confounding factors which affects individualization. Considering such potentials India need to take initiatives to develop way forward.

(2) Digitalization: Word is becoming more and more digitalized day by day. The rate with which India and China digitalizing themselves, is commendable with more faster-cheaper internet and very easy to operate mobile apps. There is need to develop rules-regulations for e-CT. Among the latest, e-clinical solutions are moving research networks to R&D cloud platforms. While these externalized networks pose security concerns for

some, the data efficiencies, transparency they create are undisputed. For instance, Japan has developed prospect for e-study data utilization. Such initiatives are also warranted in both India and China. (Figure-2)

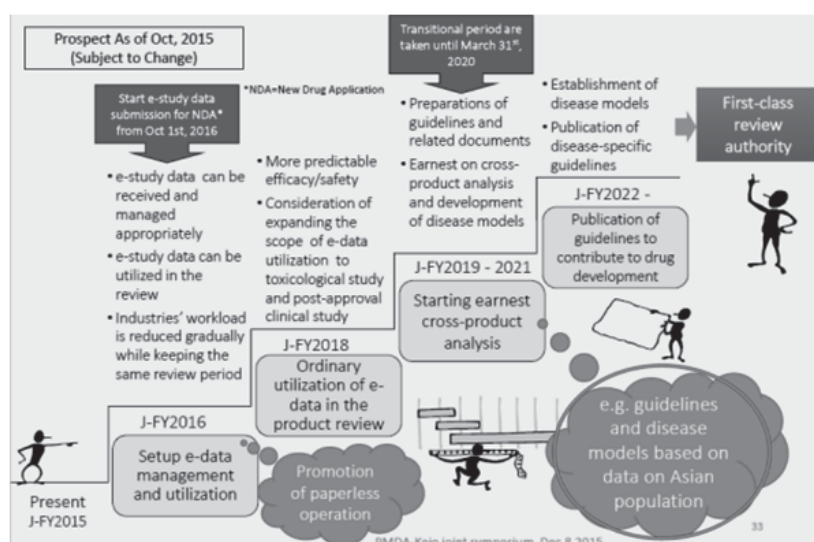


Figure 2 Prospect for e-study data utilization in CT

(A) Conclusion

Both India and China have to continuously focus on how they can increase the CT's quantity, quality, safety and GCPs in their respective countries. At every juncture related to CT, India and China are on a journey of double edge. A simple ignorance or carelessness either way may harm their probable ideal status to conduct CT irreparably.



B. V. Patel Essay Competition History at a Glance

The trust conducts an all India level Essay Competition every year as one of its activities. The selection of the subject depends on the importance and the current happenings in the Sector. Any one interested in drugs & pharmaceuticals, academically, industrially or otherwise, can participate in the competition. The entries are generally invited in the month of July/August. The essays are evaluated independently by a panel of judges comprising of the expert luminaries of industry and academy. The essays of the winners are printed and distributed during the IPC since 1977.

The year-wise subjects chosen for the Essay Competition :

Year	Subject
1977	- Good Manufacturing Practice in Parenterals
1978	- Indian Pharmacopoeia for the Future
1979	- Documentation and Record Keeping in Drug Manufacture
1980	- Drug Distribution
1981	- Review and Modification of Drugs Legislation in India
1982	- Industry Oriented Pharmacy Education - Its Means and Modifications
1983	- Role of Testing Laboratories in Assurance of Quality Drugs
1984	- Material Management in Pharmaceutical Industry
1985	- Status & Prospect Of Research and Development
1986	- Manufacture of Dosage Forms - Problems and Remedies
1987	- Advances in the Technology of Industrial Pharmacy
1988	- Role of Combination Products in Drug Therapy
1989	- 1. Continuing Education in Pharmacy 2. Trends in Pharmaceutical Research
1990	- Restructuring of Pharmacy Education
1991	- Biotechnology in Pharmacy
1992	- Role of Pharmacists on Stability of Pharmaceuticals
1993	- ISO 9000 and its Applicability to Pharmaceuticals-A Pharmacists Perception

- 1994 - Challenges and Opportunities in Pharmaceutical Research
- 1995 - New Drug Delivery Systems - Indian Scenario
- 1996 - Traditional Medicines - Sources of New Drugs
- 1997 - Clinical Pharmacy in India - Emerging Facet of the Pharmacy Profession
- 1998 - Community Pharmacy
- 1999 - Revision of Indian Patents Act 1970 And its Impact on Availability and Cost of New Pharamceuticals
- 2000 - Information Technology-Revolutionary Impact on Pharmaceutical, Sciences
- 2001 - Aesthetic Design of A Manufacturing Unit in Compliance with National Regulatory Requiriement and WHO - GMP
- 2002 - Genomics and Proteomics: Treasure for Drug Discovery
- 2003 - Pharmacy Education: Current Problems and Suggested Solutions
- 2004 - Industrial Growth in Changing Scenario: Strategic Options for Small and Medium Enterprises (SMES)
- 2005 - Roadmap to Globalization of Ayurveda as Recognized Healthcare System
- 2006 - Prospects for CRO in next Five Years: Indian Capabilities
- 2007 - Distribution of Pharmaceuticals and Drugs in India: Its Science, Commerce and Ethics
- 2008 - Medical Devices: Opportunities For Indian Industry
- 2009 - Steps to Revitalize Pharmacy Profession in India
- 2010 - Innovation: Driver for Growth of Indian Pharma ?
- 2011 - Vaccines In Healthcare: Indian Perspective And Potential
- 2012 - Drug Affordability in India - Post 2005
- 2013 - Patent - The Need for Efficient Handling of Disputes
- 2014 - Pharmacists in a State of Mortification: Reasons, Responsibilities of Stakeholders and Remedy
- 2015 - Pathway for Zero Defect Product and Production in Pharmaceutical Industry