GLOBAL Clinical Trials
CHALLENGES & SOLUTIONS...
2012

THE ASSOCIATED CHAMBERS OF COMMERCE AND INDUSTRY OF INDIA
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CHALLENGES & SOLUTIONS...

2012

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I ndia is fast emerging as an attractive destination for conducting global clinical trials. Increased globalization has brought about fundamental changes in the way clinical trials are conducted here. Increased awareness of Good Clinical Practices requirements, stronger international acceptability of research done in India has brought favorable changes in the attitude of clinicians in India towards participation in clinical trials.

By the early 2000’s, there remained two significant challenges in conducting Indian clinical trials from the western sponsor’s perspective: shaky intellectual property protection and a long, opaque regulatory process for obtaining clinical trial approval. The former has been resolved by India’s participation as a signatory in WTO’s TRIPS agreement and subsequent harmonizing amendment of India’s own patent laws in 2005. The approval problem was addressed in late 2006 when India’s regulatory authority, the Drugs Controller General of India (DCGI) and the Central Drugs Standard Control Organization (CDSCO), the Indian regulatory authority, introduced a two way track process allowing rapid approval of clinical trials that were part of a global development program.

I am glad to note that ASSOCHAM & Apheta Institute of Clinical Research has been continuously monitoring the evolution of the healthcare industry structures and has proactively come-up with this report. The area of Clinical Trials has become increasingly important for India, since there is no other way to have innovative and safe medication to enter into the market and reach the ailing patients.

I wish to thank DBT, CSIR and ICMR - the three nodal scientific research promoting agencies of the government along with the private partners for providing their support. Thanks to the ASSOCHAM Healthcare team with Dr.Tyagi, Agnideep, Sandeep and Nitesh, who have been instrumental in taking the initiative forward.

R.N.Dhoot (MP)
President, ASSOCHAM
ACKNOWLEDGEMENT

It gives me immense pleasure since ASSOCHAM with the support of DBT, CSIR and ICMR is organizing the ASSOCHAM symposium on “Global Clinical Trials – Challenges and Solutions”.

Travelling together with many dynamic members, ASSOCHAM brings forth the essence of modern business practices and unfolds the tremendous opportunity that lies underneath, especially in the field of Clinical Trials and largely in the healthcare sector. The forum had aimed to create a fine line through regulators and industry experts and bring first hand information at the disposal.

We recommend this joint study meticulously prepared by the ASSOCHAM team and Apheta Institute of Clinical Research on the subject giving a view of the present scenario of the sector to all the professionals. ASSOCHAM has been able to give an insight on the market orientation and the newer adaptive economic models by comparing it with the global demands. It has covered the various challenges in process and workflow of the clinical trials, including how a metamorphosis in policy framework could bring a possible change in the business environment.

My heartfelt thanks to the industry leaders and experienced professionals of the sector, who were an integral part of the program. Their involvement in thought leadership has made this program successful. Last but not the least I am thankful to the ASSOCHAM team with Dr Tyagi, Mr. Sandeep, Mr. Agnideep and Mr. Nitesh to bring this vibrant initiative before all of us.

Mr. D. S. Rawat
Secretary General
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Introduction

Clinical research has proven to be a boon for mankind with the consistent introduction of better and innovative drugs, diagnostic procedures and medical devices. A number of options are available today for many disorders which were considered to be incurable in the past. Unmet medical needs, downstream health cost, cost to individual country, sustenance of the pharmaceutical industry and patent expiry are some of the important factors driving the commercial organization for new drug development. However the process is not easy and fraught with risk and dangers. Time taken to develop a drug and the cost involved in it are the two most important factors encouraging the pharmaceutical and medical device companies to carry out clinical trials in the developing countries where there is scope of faster recruitment of trial subjects and cost attractiveness. This lead to the introduction of the term emerging market for clinical trials consisting of the countries like India, China, Brazil etc. which are found to be hugely successful markets. Thus the trend off shoring and outsourcing of clinical trials surfaced in 2002 and has been on a rise since then with evolution of large number of contract research organizations in such countries.

Even though this trend has been beneficial for the sponsors of the new innovations as well as the emerging hubs of clinical trials but there are a number of challenging aspects which has come into the light. We are provided with the opportunity in this knowledge paper to elaborate some of the most evident of the challenges of global clinical trials from each of the stake holder's point of view and as relevant for India. We have also suggested solutions and recommendations with respect to the challenges which can help India to become the most optimal clinical trial zone among its adversaries.
patients. There is also no language barrier along with availability of many tertiary care and specialty hospital.

According to the www.clinicaltrial.gov below are some data with location and number of trials.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>11 studies</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>113 studies</td>
</tr>
<tr>
<td>India</td>
<td>2032 studies</td>
</tr>
<tr>
<td>Nepal</td>
<td>27 studies</td>
</tr>
<tr>
<td>Pakistan</td>
<td>191 studies</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>25 studies</td>
</tr>
<tr>
<td>China</td>
<td>2926 studies</td>
</tr>
</tbody>
</table>

**Clinical Trials in Asia**

![Bar chart showing clinical trials in Asia](Ref: clinicaltrial.gov)

India is considered to be the most important clinical trial market among the emerging countries. According to Mckinsey & Company Indian Clinical Research a market value is of 1.5 billion USD attributed to US and European Sponsors by 2010. This revenue is expected to be about 20 billion USD by 2015 in India and it comes within the top 10 markets of the world. The encouragements by the government lead to its fast growth as world player with a supportive regulatory framework initiative. Factors driving the increase of CRO investment in India include an improvement in the clinical trials regulations, strong emphasis on research and development among Indian pharmaceutical companies and the attractive cost advantage.
of about 30% - 50% over the United States in performing clinical trials activities. At present this industry in India demands for more than 10,000 GCP trained investigators.

**Evolution of Clinical Research in India**

The Indian clinical trial industry was at the budding stage during the 90’s with only a few trials conducted in India by the pharmaceutical and biotech companies of USA and Europe due to lack of infrastructure, patent protection and regulatory obstacles. The government of India realized the potential of the industry to develop into a premier one and in January 2005, amended the Schedule Y of the Drugs and Cosmetics Act of India to upgrade it to the standards of FDA in order to harmonize it with US and International Conference on Harmonization. These changes together with development in infrastructure and training of clinical research professionals lead to a boom in the field of clinical research in India. The growth of pharmaceutical industry of India is aiding the advancement of the clinical research. Presently enormous amount of clinical research activities have been outsourced to India which has lead to the development and establishment of CROs by the global as well as Indian entrepreneurs. The activities which initiated only with clinical operations, now consist of almost all the aspects of clinical research including data management, protocol designing, biometrics, quality assurance to name a few.

The graph gives us a clear picture that most of trial related activities are performed in India and not only restricted to clinical operations. Below mentioned are the different sectors related to clinical research and also their growth percentage.
Percentage of different models emerged in Clinical Trials

Clinical Research Training institutes 7%
Pharmaceutical Companies 20%
Clinical CRO (global) 13%
Site Management Organization 3%
Clinical CRO (local) 13%
BA/BE CRO 7%
Discovery/Chemistry CRO 12%
Data Management CRO 13%

The future Indian scenario

India implemented product patents in 2005. This product patent protection has encouraged multinational companies to import technology into India to develop new products. These developments will create new opportunities for the pharmaceutical and biotechnology companies to conduct clinical trial of their products in India. Sponsors are looking at India to leverage the high cost of trials in the U.S. and Europe, and also reduce the time to market the drug. The clinical trial market in India is expected to grow at 10%, then by 2015 there will be a demand of 50,000 clinical research professionals. India has a large number of qualified scientists, pharmaceutical and medical graduates but the number of trained clinical research professionals is few in number. This has created a supply & demand gap for the professionals. On the path of developing India as a global leader in clinical trial market, greater attention is required for the development and training of the research professionals.
There is an increasing demand of trained investigators as trials are being conducted in every therapeutic area in India. Lack of experienced & ICH-GCP trained personnel is one of the concerns for India, which can be conquered with good training programs designed for the medical as well as life science graduates.

**B. Market- Analyses & Strategies**

**India**

In visualizing India as a global player of clinical trial market, few of the quotes in this context are worth mentioning like-

“Broad regulatory reforms, a sizable and growing pharmaceutical market, combined with highly attractive professional and patient populations, make India a compelling new region for conducting global clinical trials.”

CenterWatch (Aug 2003)

“India’s business and regulatory climates have undergone dramatic change in the past few months through passage of a patent bill, regulations updated to harmonize with TRIPs and international standards, and plans for a more US FDA-like regulatory body.”

CenterWatch (July 2007)

**Clinical Trials in India and worldwide**

![Clinical Trials in India and the world](Ref: www.clinicaltrial.gov dec 2011)
Growth of Clinical Research industry

The above graphs gives an idea about the number of clinical trials being conducted in India and also about the revenue generated by it. According to Mckinsey & Company India can attract between 5 -10% of the global contract research outsourced market (all services including chemistry, toxicology and clinical research) over next 5 years.

The Indian pharmaceutical industry is growing at an annual rate of 11% while the clinical research industry is growing an annual rate of whopping 84%.

Market value for clinical trials outsourced to India is estimated at around $300 million, having increased by 65% in 2006, it has touched to $1.5-2 billion by 2010 and foreign sponsors spend USD 300M+ on clinical trials in India.

Clinical Trial Capacity of India

Many factors contribute in India’s emergence as the hub for clinical trials. The following illustration gives us an idea about the important factors and its level of competence in India, which makes it a heaven for the sponsors of clinical trials.
<table>
<thead>
<tr>
<th>Patient Pool</th>
<th>Scanty</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. Recruitment Rate</td>
<td>Lowest Rate</td>
<td>Highest Rate</td>
</tr>
<tr>
<td>Speed</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cost</td>
<td>Most Expensive</td>
<td>Least Expensive</td>
</tr>
<tr>
<td>Facility &amp; Investigator Pool</td>
<td>Smallest Pool</td>
<td>Highest Pool</td>
</tr>
<tr>
<td>Industry Trial Experience</td>
<td>Least Experience</td>
<td>Most Experience</td>
</tr>
<tr>
<td>Regulatory Environments</td>
<td>Least Conducive</td>
<td>Most Conducive</td>
</tr>
<tr>
<td>Quality of Data</td>
<td>Unacceptable to EU/US</td>
<td>Acceptable to EU/US</td>
</tr>
</tbody>
</table>

**Comparison of India with other emerging and established markets of clinical trial**

If we compare the emerging markets of clinical trials like India, China with that of the mature markets like United States on the basis of its patient pool, cost efficiency, regulatory condition, relevant expertise and infrastructure and environment, it shows to be an attractive
market being an emerging one for the conduct of clinical trials. Though the score for each of the categories may vary but it scores high with respect to patient pool and cost efficiency to the mature markets.

### Overall country attractiveness index

<table>
<thead>
<tr>
<th>Country</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>6.10</td>
</tr>
<tr>
<td>India</td>
<td>5.58</td>
</tr>
<tr>
<td>Russia</td>
<td>5.55</td>
</tr>
<tr>
<td>Brazil</td>
<td>5.26</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>5.00</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5.00</td>
</tr>
<tr>
<td>Argentina</td>
<td>4.90</td>
</tr>
<tr>
<td>Poland</td>
<td>4.84</td>
</tr>
<tr>
<td>Hungary</td>
<td>4.81</td>
</tr>
<tr>
<td>Germany</td>
<td>4.69</td>
</tr>
<tr>
<td>South Africa</td>
<td>4.56</td>
</tr>
<tr>
<td>Taiwan</td>
<td>4.46</td>
</tr>
<tr>
<td>Israel</td>
<td>4.28</td>
</tr>
<tr>
<td>Singapore</td>
<td>4.27</td>
</tr>
<tr>
<td>Ireland</td>
<td>3.86</td>
</tr>
<tr>
<td>United States</td>
<td>6.83</td>
</tr>
</tbody>
</table>

**Scale:** 1–10

Source: A.T. Kearney

Notes: Higher scores indicate higher levels of attractiveness. The 15 countries analyzed were selected based on size, diversity and geographical distribution. The Index is not meant to be comprehensive across all potential offshore locations.
2. Regulatory Struggle

Overview of Regulatory process for conducting a Clinical Trial in India

Clinical trials in India are regulated by DCGI through Schedule Y of the *Drug and Cosmetics Rules, 1945*. The *Rules* were revised in 2005. Schedule Y defines the requirements and guidelines for import and/or manufacture of new drugs for sale or for clinical trials.

For conducting a Clinical Trial in India the sponsors should have the written permission from the DCGI and IRB. Form 44 (Clinical trial application Form) is used which is accompanied by all the documents such as chemical and pharmaceutical information, animal toxicology data, Clinical Pharmacology data with other trial related documents such as Investigator Brochure, Protocol, Case Report Form, Informed Consent form, Patient Information Sheet & Investigator Undertaking and the trial’s Regulatory status in other countries.

In Schedule Y application for permission to conduct a clinical trial must be accompanied by a filing fee which is either Rupees Rs 50,000 (~$1200) for a phase I trial (called Human Pharmacology Study); or Rs 25,000 (~$600) for a phase II (Therapeutic Exploratory Study) or a phase III study (Therapeutic Confirmatory Study), after this the DCGI reviews it. Once written approval of the Schedule Y application is obtained from DCGI and an IEC, clinical trial may be initiated.

**Regulatory Timeline in India**

<table>
<thead>
<tr>
<th>Regulatory Process</th>
<th>Approval</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCGI</td>
<td>For conduct of clinical trials (all phases)</td>
<td>First response or approval within 45 working days</td>
</tr>
<tr>
<td></td>
<td>For conduct of bioequivalence study</td>
<td>28 working days</td>
</tr>
<tr>
<td>IEC/IRB</td>
<td>IEC approval for various site study</td>
<td>4- 6 weeks (in parallel)</td>
</tr>
<tr>
<td>DCGI</td>
<td>Test License to import supplies</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Any file sent to referral bodies/sent for expert opinion</td>
<td>IND applications for rDNA products, radiopharmaceuticals, stem cells, etc</td>
<td>Additional 12 to 14 weeks</td>
</tr>
</tbody>
</table>

*Clinical trials approvals can stretch to 14 weeks in certain cases*
Regulatory Struggle in India for conducting a Clinical Trial in India

The regulatory bodies have to elevate themselves to meet international standards. Few of the major points for improvement are discussed below.

a. Foreign first-in-human trials of New Chemical Entities in India is not permitted to be conducted in India. Those which are co-developed in India is permitted but takes a long time for approval.

b. The approval timeline for conducting clinical trial in India is lengthy when compared to the US FDA. Here it takes about 5-8 months for the approval of new chemical entities whereas it is only 30 days with US FDA for the same trial.

c. The Clinical Trial application which is submitted to DCGI, the DCGI office does not having the competency to review such protocols, sometimes they are referred to outside agencies i.e. the ICMR, the BARC, the DBT, the AERB and/or the GEAC for their review and expert opinion, which results in longer review times, which causes additional time involves. So expert committee are constituted to review the protocol & other related documents.

a. Inadequate interaction between the Regulatory Authority and the Sponsors/CRO which is required to enhances the understanding of the regulatory authority requirement and develop a relationship between the sponsors and regulators.

b. There is an increase in the number of applications for approval of Clinical Trials in India, but no increment in review staff of DCGI. This has resulted in the DCGI office facing serious problems related to manpower which is in turn causing an increase in timeline for the review and approval of Clinical Trials.
3. Sponsors Implications to conducting a Clinical Trial

A. Overview

A clinical trial sponsor is the company or organization which conducts a clinical trial. It can be an individual, company, institution, or organization that takes responsibility for the initiation, management, and financing of a clinical trial (according to ICH-GCP).

Clinical trials are sponsored by government agencies, private organizations, and individual researchers who are seeking ways to improve the health of people living with chronic and life-threatening illnesses. Sponsors include: (by FDA)

- Government agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veteran's Affairs (VA), WHO, ICMR and NGO foundations.
- Pharmaceutical, biotechnology and medical devices companies
- Individual researchers
- Health care institutions such as academic medical centers and health maintenance organizations (HMOs)

Clinical trials take place in a variety of locations, including hospitals, universities, doctors' offices, or community health clinics.

Clinical trials are powerful weapons which need to be handled with care. They permit us to test the clinical hypothesis generated by the sponsors to test on human subjects and they have the potential to change the standards of care. The economic result of such changes can be considerable. Well-done trials, published in distinguished journals, may be used to market drugs and medical devices, potentially resulting in massive financial boost for the sponsor. But powerful tools must be used carefully.

Sponsors are not only vested with the responsibility of providing funds for the clinical trials but also have various other obligations. The current trend in the field of research is globalization of clinical trails. Sponsors who mainly hail from the developed parts of the world are outsourcing and conducting large number of trials in the developing countries like India, Brazil which increases its culpability. They have the liability of human life on themselves from a foreign country. They are responsible for selecting the investigators & institution. Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented.
(recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. Matters related to compensation and indemnification also rest on the sponsors. The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement. The sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial. Sponsors should provide with the medical expertise who will be readily available to advise on trial related medical questions or problems. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

One of the main activities of the sponsors is its dealing with the regulatory authorities. As trials are now conducted around the globe, they have to gain approvals from a large number of authorities depending on the countries they want to conduct trial. Approvals for the conduct of trial, export of the laboratory samples and import of investigational trial drugs are some of the areas where the regulations differ with each country.

One of the important roles of the sponsor is handling of the investigational product. When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and clinical trials are available to support human exposure. Sponsors are responsible for the manufacturing, packaging, labeling, and coding Investigational Product. The clinical trials supply chain which one of the problem areas for present globalize scenario also rest on the investigators.

Some of the pharmaceutical and biotechnology companies which invest in clinical trials include Pfizer, Hoffmann-La Roche, Novartis, Takeda Pharmaceutical Company, Eli Lilly and Company, GlaxoSmithKline, AstraZeneca, Sanofi S.A, Merck & Co etc.

The globalization of clinical trials has resulted in a number of challenges for the sponsors. Both time and cost in drug development have driven them to the emerging markets like India and China. This has brought financial benefit for the sponsors on one hand and evolution of hurdles on the other. Some of the areas of concern for the sponsors are discussed further.

Undertaking a clinical study with international sites can be a daunting task. However, by being proactive, diligent and thoughtful during the initial planning process, sponsors can help to ensure their study is a success.

B. Regulatory Deterrents

The globalization of clinical trials has focused us towards the challenges that come in the way of a successful clinical trial. Among many of the hurdles that will be discussed later, the
foremost is the regulatory consideration. The problems associated with different countries will vary from country to country for the sponsors, but we have chosen some of the areas of concern related to India when conducting a clinical trial.

**Timelines**

The clinical trial applications are submitted to the Drugs Controller General of India (DCGI) for approval, and are regulated under Schedule Y, which was updated in 2005. The regulatory approval process in India was streamlined in 2006, such that regulatory approvals for clinical trials that have been previously approved in certain countries including the United States, Europe, and Japan usually take about three months. Clinical trials that have not been previously approved may take considerably longer, and timelines are often unpredictable due to bureaucracy and additional regulatory requirements. Moreover like the US FDA and EMEA, the regulatory authority of India does not provide any guidance document on the current interpretation of the regulatory requirements.

**Categorical Testing**

The investigational product depending on whether the drug undergoing testing is categorized as a biologic or a genetically engineered product, additional approval from other agencies such as the Indian Council of Medical Research (ICMR), the Genetic Engineering Approval Committee (GEAC), and the Department of Biotechnology (DBT) is necessary and can take up to six months. Submission to Ethics Committees can be done simultaneously.

**Difference in GCP**

Although the regulatory approval process in India has evolved considerably, many issues remain. In large part, this is because India’s Ethical Guidelines for Biomedical Research on Human Subjects were established relatively recently as were the Indian GCP guidelines, 2000 and 2001, respectively. However, sponsors should be aware of differences in the Indian GCP version of ICH-GCP, including the Indian specifications for the composition of the Ethics Committee, informed consent procedures, and patient compensation for participation. In addition, sponsors should be familiar with the Indian GCP specifications concerning the role and responsibility of foreign sponsors conducting clinical trials in India.

**Phase I trials**

There is reluctance in some countries to have ‘first in man’ studies conducted before the source country, which precludes parallel development of early clinical stages. For the investigational drug developed outside India, the sponsors will not be permitted to carry out Phase I studies in India. This can be attributed to inadequate experience of regulatory, scientific and ethical issues for Phase I studies and delay in regulatory and ethics approval of Phase I trials. The investigational drugs which are co-developed in India or solely developed in India will get approval to conduct phase I studies.
**Sponsors Approach**

Companies need to plan their global development strategically, including allowing a reasonable time for necessary processes, such as translations. They are responsible for being aware of local regulatory requirements and should focus on essential issues. Companies need to be prepared to talk with regulators and to base their discussions on scientific rationale. They need to facilitate discussions amongst regulators by recognizing the constraints of confidentiality and giving permission, when required, for the exchange of assessment information.

Consideration of a CRO is the powerful solution for the sponsors in overcoming the regulatory challenges of a country. A CRO who has the expertise in handling the regulatory affairs & ethical issues of a country is the most vital tool for the sponsors to conduct a successful clinical trial. They will be aware of the present regulatory amendments, political scenario and ethical considerations of the country. This will help the sponsors to plan the study taking into account the lengthy timelines for the regulatory approvals of the country. Difference in the GCP is the other issue which the sponsors need to take care of which can also be done with the help of a local CRO. They have a good idea about the ethics committee composition, informed consent procedure and the different ethical and regulatory submission requirements and timelines.

**C. Budgeting**

The financial aspect of a global clinical trial needs to be focused because of the number of issues rising out of it during its operations. The clinical trial is the most crucial stage of drug development and also the most expensive one. The fate of a new drug depends on its success which is related to large number of people associated with it. The most relevant of the financial problems encountered by the sponsors during the conduct of a global clinical trial is highlighted below.

**Contracts**

Clinical trial agreements play a vital role in the financial management of a clinical trial. When it is associated with a global trial, sponsors need to be more careful while framing it because of a difference in the financial transactions of every country. If proper negotiations are not done between the institute and the sponsor, might lead the sponsors to a financial loss. The important financial content of a clinical trial agreement includes indemnity by the sponsors & insurance for the patients. The legal policies of every country are a concern for the sponsors. If problems arise in the indemnity or in patient compensation, the site might not be able to continue with the trial further. The sponsors will have to terminate the site which is not only a loss of sponsor’s resources but also time.
Equipment & cost of clinical trial supply

Clinical trials in the emerging countries of the world bring a lot of advantage for the sponsors. But the sponsors should also be ready to bear the additional cost in maintaining of the clinical trial supply. Equipment and supply costs for the performance of industry-sponsored clinical research may include such items as phlebotomy supplies, centrifuges, freezers, computers, software, laboratory notebooks, and copy/fax machines. Today trials are conducted around the globe, with this the expenses in maintaining the clinical trial supply has also increased. Greater emphasis needs to be given in the manufacturing, packaging, labeling & handling of the investigational drug. Maintaining the drug in the optimal temperature, shipping of the drugs to the sites incurs additional cost for the sponsors. Hot and humid climatic condition of India provides a challenge in maintaining the optimal cold chain of the drug.

Laboratory expenses

The samples which are required to be tested in the central laboratories might be an added burden for the sponsors. The central laboratories are mostly located at a distant country from that of the site. The samples need to be carefully collected, packed and shipped to the central laboratory. If problems arise with the sample, there would always be the requirement of recollection and shipment of the sample which will add to the cost.

Trial Management Software

Use of manual processes to merge large amounts of complex, disparate data to produce a comprehensive analysis of each trials operational and financial performance are no longer applicable in these times of complex global clinical trial designs. There is the requirement latest software in data collection & management. Credible data is the ultimate aim for the sponsors of any clinical trial which would only be possible with the electronic format of CRF & Patient reported outcomes. But these soft wares are expensive with high validation & maintenance cost. For e.g. handheld device diary solutions have significant startup fees. Hardware must be purchased or leased, configured, assembled and shipped before subjects can enter data. Incase of IVRS there is the cost of call volumes i.e. the length and frequency of patient diary calls.

Regulatory & Ethics committee fees

The current trend of conducting a trial in a large number of sites in different countries of the world can add up in the cost for the sponsors. The regulatory fees for review & approval of the protocols, permission to import of trial drug to the country and export of laboratory samples are some of the significant costs in this area. Along with it the number of sites selected in a country by the sponsor will have their own Ethics committee for most of the institutions. The sponsors will have to take approval from them which have their own review fee.
Monitoring & Auditing

The quality of a clinical trial is dependent on the level of monitoring & auditing undertaken by the sponsor. The frequency of monitoring depends on the complexity of the trial. Trials are scattered in different sites in a single country. So there is a significant travel and accommodation expenses of the monitor to be considered by the sponsor.

Investigators Meeting

A clinical investigator meeting is given by a clinical trial sponsor to conduct protocol and GCP training and allow participants an opportunity to ask questions about clinical trial conduct. The meeting typically includes clinical research associates, clinical research coordinators, clinical investigators, medical monitors, quality assurance and senior management. Such meetings are a costly affair as the sponsors provide for the travel, accommodation & food for a large number of trial members in a foreign location.

Inflation

Clinical trials are a lengthy affair in drug development. Usually takes years to complete the present unstable economy with inflation rates rising in most of the developing economies like India can topple the planned budget for the sponsors.

Staff Labor and training

Staff labor and training usually represents the largest single line item of an industry sponsored clinical trial budget. It is also the hardest portion of the budget to estimate, and is potentially the greatest source of error. Furthermore, salaries for staff labor and training vary widely among different geographical areas and countries.

Patient Follow-up

Because of the importance of obtaining patient follow-up data, most sponsors are willing not only to negotiate the cost of staff labor, but also the cost of such items as patient transportation, meals, parking, and outpatient clinic fees. Additionally, many sponsors are willing to pay to send an investigator’s staff member directly to a patient’s residence to obtain patient follow-up data.

Solution

The competitive nature of today’s clinical research climate can make the planning and negotiating of study budgets and contracts stressful, time consuming and full of pitfalls. Successful budgeting for the performance of an industry-sponsored clinical trial thus requires a thorough understanding of the direct and indirect costs associated with performing clinical
research which is common to every country and also the difference in the fiscal & legal issues pertaining to every country. While some of the points mentioned above are inevitable in conducting a global clinical trial. Sponsors can contain some of the issues with a thorough individualized planning for the countries and framing the budget with the financial experts. The use of the Clinical trial management system will also prove to be a boon for the sponsors as it also encompasses trial data such as documentations (protocol, CRFs), patient recruitment and enrollment, investigator relationship management, monitoring, reporting and cost tracking. It is a single website and credential for all studies being conducted for a sponsor. The main utilization of CTMS is in financial management and clinical supply management. Financial management includes tracking study costs, reimbursing investigators and paying claims related to study activities. Clinical supply management includes supply tracking, storage and shipment. The goal of a clinical trial management system is to facilitate the planning, execution and tracking of relevant clinical trial activities.

D. CRO consideration

Outsourcing of clinical trials to contract research organization is the important aspect of the current globalize scenario of clinical research. Sponsors often use contract research organizations (CRO) to help conduct, monitor, and manage research. CRO expertise and manpower potentially can be valuable particularly in global studies. Study management is a complex undertaking in any clinical trial, but considerably more so for large, multi site trials being conducted in developing countries. Simply having sites in more than one country (whether developed or developing) means that individual investigational sites may be many hundreds or thousands of miles apart. The contract research organization (CRO) selected to conduct the study has to have a impression in the selected countries. Regulatory, cultural, linguistic barriers have all contributed to the development of CRO trend in the conduct of global clinical trials. Below are some of the key areas of pitfalls in CRO consideration.

Experience

The experience of a CRO in managing a clinical trial plays a important role in the success of a trial. There a large number of CRO’s emerging in countries like India. This culture is on a rise. Small and large firms bid for the projects from the pharmaceutical companies. Many of them promise to provide a cost effective solution for the clinical trials. But the sponsors need to be careful while selecting a CRO because sometimes a new firm offering services at lower rates can cost sponsors dearly in the longer run. Lack in experience also hampers the timely completion of the trial activities for the sponsors.

Effective monitoring

Along with an experienced CRO, what is important for the sponsor is the availability CRA’s who can perform effective monitoring. Effective monitoring of clinical trials is very important in securing the quality and integrity of study data. Clinical Research Associates (CRA) must be experienced in source document verification and assessment of case report
forms (CRF). Moreover, CRA’s need to be effective communicators and accurately report findings back to the sponsor. Many CRO's employ beginner CRA’s with limited field experience, whom could be recruited economically. This may sometimes result in the replacements of the staff. Once a project has started and especially after half completion, re-training of replacement staff due to recruitment efforts will prove costly to a sponsor, as well as jeopardizing superior and timely submissions. This is a problem in India because there is a huge gap between the supply and demand of experienced CRA.

**Electronic capabilities**

Electronic systems, often referred to as eClinical technologies, provide an essential framework that support a variety of processes necessary for the successful conduct of clinical studies. The organization which is not well versed with the current technologies can create complexities for the sponsors in trial management as the amount of data generate is huge in the present scenario. Electronic Data Capture (EDC), Interactive Voice Response Systems (IVRS), Clinical Data Management Systems (CDMS), Clinical Trial Management Systems (CTMS), as well as many other clinical data collection systems such as EKGs, labs and imaging technologies are important time savers and now the standard for larger trials. CRO’s which are not flexible in the adoption of current technology, considering them will be a huge loss for the sponsors.

**Work load**

It is important for the sponsors to consider the current amount of work being undertaken by the CRO. Number of studies a CRO is concurrently administering, as availability and consistency of staff will be challenged, thereby risking regulatory compliance and quality. Similar trials in same therapeutic area will the sponsors to loose its advantage of timely completion of the trial.

**Points for sponsors to consider in selection of a CRO**

Evaluate the sophistication of Electronic Study Tools (e.g.: eCRF, IVRS, e-tracking).

Consider their flexibility and adaptability

Sponsors need to assess the cost versus quality of the CRO and the timeliness of their activities so that the sponsors have credible data on time.

Verification of duration of industry experience, along with therapeutic expertise should be confirmed for the CRA, project management team and the medical affairs group as well as the CRO.
E. Inadequate Intellectual Property Rules

Intellectual property rights are the rights awarded by society to individuals or organizations principally over creative works: inventions, literary and artistic works and symbols, names, images and designs used in commerce. They give the creator the right to prevent others from making unauthorized use of his/her property for a limited period. Patent is an intellectual property right is an exclusive right awarded to an inventor to prevent others from making, selling, distributing, importing or using his/her invention without license or authorization for a fixed period of time. Factors that determine patentability of an invention are novelty, non-obviousness and utility. Though India amended its Patent Act in 2006, it still a concern for the foreign countries specially those conducting research in India.

The United States has placed India among most severe category of countries and blamed of not providing an adequate level of intellectual property rights protection. The annual "Special 301 Report" by the office of US Trade Representative has included India among the 48 countries that have been retained in the Priority Watch List 2006. India made some improvements to its IPR regime during the past year but IPR protection concerns remain due to inadequate laws and ineffective enforcement, the USTR said in the report.

Foreign countries often urges India to improve its IPR regime by providing stronger protection for copyrights, trademarks, and patents as well as protection against unfair commercial use of undisclosed test and other data submitted by pharmaceutical companies seeking marketing approval for their products.

India improved its patent protection regime when it passed legislation in early 2005 was a positive step to provide for product patents for pharmaceuticals and agricultural chemicals but is still at a vulnerable state with a weak law and enforcement system. The foreign owners experience difficulties in obtaining the benefits of IPR due to procedural barriers and delay. It has been pointed out also that India's criminal enforcement of IPR is weak, the deficiencies in a number of areas including border enforcement, judicial dispositions and imposition of deterrent sentences.

Data exclusivity

Data exclusivity provides protection to the technical data generated by innovator companies to prove the merit of usefulness of their products. In the case of pharmaceuticals, it means the data generated by drug companies through expensive global clinical trials to prove the efficacy and safety of their new medicine. By gaining exclusive rights over this data, innovator companies can prevent their competitors from obtaining marketing license for low-cost versions during the tenure of this exclusivity.

Indian drug firms that make generic versions of innovator medicines get their approvals after proving that their product is bio-equivalent to the original drug. In other words, they do not
repeat the same clinical trials conducted by the innovator company to generate data needed to prove its safety under current laws.

Data exclusivity is in originator of a drug when let to protect the data submitted by him to the regulatory authority against unfair commercial use. During the period of data exclusivity the data can be protected from being cited by the subsequent applicant for requiring marketing approval. This proves to be a serious implication for pharmaceutical companies where substantial amount of data is generated during discovery and development of a new drug. The data is in the form of clinical trials data, reports of pharmacological and toxicological profile of drug, its use and indications etc. This data which is submitted to regulatory authorities of concerned countries for marketing approval is generally referred by regulatory authorities for approval of generic medicine. Multinational companies based in developed countries argue that this data generated during drug discovery and development needs to be protected in the form of ‘data exclusivity’ which is mandated under Article 39.3 of TRIPS Agreement. Developing countries state that ‘data exclusivity’ is not mandatory according to TRIPS Agreement. So far India has not provided for ‘data exclusivity’. India’s position on ‘data exclusivity’ with respect to other countries of the world is subject to recommendations and suggestions of the committee set up by the Government of India to look into issue of ‘data exclusivity’.

The most serious impact is likely to be on drugs that are not under patent. In such cases, data exclusivity will create a “patent-like” barrier that will prevent generic entry of new formulations during the entire period of exclusivity. A good example cited of its benefit involve traditional medicine ‘colchicine’, which cannot be patented as it has been used as a therapeutic agent in the treatment of gout for thousands of years, was awarded data exclusivity in the United States. Once the US drug regulator accepted the one-week trial of the drug, the company was able to enforce data exclusivity to block affordable generics. It enforced its exclusive rights, raised the price from $0.09 per pill to $4.85, and sued to remove other competitors off the market. Global pharmaceutical giants say data exclusivity is essential for their future investments and research on developing country needs. It will also make companies do clinical trials before they launch their products thereby ensuring patient safety.

F. Legal Agreements

Most pharmaceutical companies conduct global clinical trials to reduce costs But keeping a look at the current situation cost is not, however, the primary driver for the globalization of clinical research: Low site fees are outweighed by high communication and logistics costs. The primary inducement is generally subject availability and also the data generated in the developed countries is found to be credible.

High volume of legal and regulatory regimes offsets these advantages, and can develop into serious complication for multinational trials. Clinical trial agreements are a tiny zone of the legal and regulatory collision that will grow in importance as globalization of the industry
continues. In the United States, it takes clinical trial sponsors an average of 35 days to negotiate clinical trial agreements (CTAs) with community-based sites and site management organizations, and 96 days with academic centers. Investigative sites have stated that the delay in negotiations in Clinical trial agreement as a cause of delay more than subject recruitment. New drugs can generate revenue of over USD1 million per day, so the cost of these delays adds up quickly. In addition, most new drugs enjoy patent exclusivity for only a few years at best, so time is of the essence.

In clinical trials, some of the delays occur when the sponsor is in one state and the site is in another. The difficulties are increased when the sponsor or site is outside the country. It is aggravated further when sites are in multiple countries. It is also increased when sites and sponsors on multiple trials are in multiple countries. It is aggravated still further when sites and sponsors are in multiple states and provinces within multiple countries. With the steady globalization of clinical research, these difficulties will become ever more onerous.

CTA addresses certain issues like indemnification, compensation for the participants, publication rights and confidentiality, IP Ownership etc. In India an improper drafting of CTA can put the stakeholders in significant liability on the account of improper disclosure, conflict of interest, ethical violations and due to trials not conducted according to GCP. A survey conducted reveals that there are disapproval on many aspects of the CTA like only 24% would agree to allow the sponsors to insert their own statistical analysis and 47% would disallow it. Fifty per cent would allow the sponsors to draft the manuscript while 40% would disallow it. Forty-one per cent would allow the provision of prohibiting the investigators from sharing data with third parties after the trial is over, 34% would disallow it and 24% were not sure about their stand. Sponsors value their intellectual property (IP) and want to protect their interests for as long as possible by keeping their IP confidential. Investigators in general and academic institutions in particular, often participate in clinical trials for the purpose of education and publication rights since this enhances the reputation of the investigators and the academic center. These positions are antagonistic to each other. Language of CTA is another barrier for the sponsors in drafting a CTA for foreign sites.

Solution

A comprehensive study of a country’s legal system and the culture of medical practice should be studies in drafting a CTA. It is advisable to include a legal expert from the country where the trial needs to be conducted who have the requisite knowledge base within them to support both clinical knowledge and legal knowledge, as is required for CTA negotiations It is important that any party that participates in the negotiation develop its checklist, determine its BATNA, and get to know the other side. The Best Alternative to a Negotiated Agreement (BATNA) is a technique developed by negotiation researchers Roger Fisher and William Ury of the Harvard Program on Negotiation. The BATNA technique proposes that before starting a CTA negotiation, it is always best for each party to know what opportunities the negotiating party would give up so that the other party can participate in the trial.
G. Sustaining Clinical Trial Supply Chain

The global clinical trials post a challenge for the sponsors in sustaining the demand and also the quality of the investigational product. Below are some of the hurdles that are faced by the sponsors in management of the global clinical trial supply management.

Catering to the site need

The major technical challenges in executing a clinical trial materials supply chain are to cater to the demands from clinical sites, so that patients are sufficiently supplied once they are enrolled while curtailing oversupply since unused materials cannot be supplied to other sites due to regulatory restrictions. Not only is patient enrollment highly unpredictable, but qualm also appears in manufacturing and shipment lead times, in process failures and in production yields. Moreover it is more costly to manufacture investigational products compare to standard drugs, so over production can also affect the sponsors as it would lead to wastage and loss of money.

Cold Chain Challenges

The storage, handling, and distribution of temperature sensitive drugs represent an increasingly imperative element of the global clinical supply chain. Clinical trials are being run on a global scale and in some cases in countries with less than quintessential support system. The complex clinical supply chain creates a challenging distribution environment because of shipping large volumes of refrigerated patient kits worldwide while maintaining and documenting appropriate environmental conditions. The temperature requirements vary with different protocols. The product passes through various time and temperature zones of the world. With large number of countries along with many sites in a country, there is increased complexity for maintaining product quality and alleviating the risk of thermal digression.

Cold chain failure may lead to following risks:

1. The patient could be administered an unsafe product
2. A lack of compliance with global regulatory and standards based requirements can increase liability for the sponsors
3. Temperature variability can lead to inconsistency of results between and within batches
4. The shipment can be rejected by the Quality department therefore leading to costly delays – increasing the complexity of trial management
Major regulatory inclination:

1. Accountability for the cold chain ultimately resides with the Manufacturer but
   responsibility is shared across all supply chain partners

2. Increased oversight, management, and control of environmental conditions across the
   entire supply chain

3. Increased importance of temperature control and monitoring

4. Amplification to the focus on the products quality with the aim of ensuring subject safety.

Partner warehouse in-country

Storage of drugs is warehouse is benefiting for the sponsors as it would make the supply
system convenient for them. But in India warehouses are available and trial drugs storage
provided by the pharmaceutical companies who also have generic drug manufacturing. This
can be seen as a risk for the foreign trial drug companies.

Environmental conditions

Environmental conditions like extremely hot weather conditions, torrential rains, natural
disasters and an unfamiliar national holiday schedule are all factors that could affect supply.
This is true especially for India as it has diverse climatic condition which differs region wise.
The number of national holidays is also another factor affecting the clinical trial supply in
India.

Courier system

In India it is a practice for couriers to arrive at depots to pick up cold chain dispatch using
their own shippers. The couriers then pack the boxes themselves and use their own ice packs
and while in course the couriers will change the ice packs to maintain the cold temperature
required .In other parts of the world there is warehouse packing and sealing a authorized
shipper has been emphasized to retain the required temperature for a specific amount of time.
This practice is seen to prevent temperature deviation which is not done in India.

Solution

As a result of the impact of the complexities of clinical trial supply faced by the sponsors in
the conduct of global clinical trials, a method has been developed for the prevention in
shortage and wastage of trial drugs. It is known as Simulation based optimization approach
using a computer program, which does demand forecast of the trial drugs. Thus helping
proper planning in the management of clinical trial supply system.
Sponsors can take the assistance of the local experts who has a global experience in the management of clinical trial supply and having validated systems and process that ensures

- Proper packaging solutions for different specific thermal ranges
- Provides temperature monitoring during transportation
- Adequate know how of the custom paper work of a country
- Provides real time tracking & related reports of the consignment
- Taking responsibility and providing solutions for associated problems in the supply chain.
4. Project Management issues- Contract Research Organization

Outsourcing and off shoring of clinical trials have led to the development of CRO’s in countries like India. The CRO industry, by specializing in clinical trial management, often performs the needed services with a higher level of expertise or specialization at a faster pace and at a lower cost than a biopharmaceutical company could perform such services internally. The key driver of outsourcing is to enhance the performance of R&D investments by achieving greater R&D effectiveness, reducing costs and expediting time to market for new medications. To achieve this goal is a challenging task; few of the areas of concern have been elaborated by us in this regard.

A. Effective Monitoring & Site access

According to ICH-GCP monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements. The person in charge should be appropriately trained, have scientific and clinical knowledge needed to monitor the trial. Qualifications of the monitor should be documented. Monitors should be familiar with the investigators brochure, the protocol, the informed consent, the sponsors SOPs, GCP and the applicable regulatory requirements.

Monitoring is the most important part of project management by a CRO. It is mainly conducted to verify that the rights and well being of the human subjects are protected. Also to make sure that the reported data are accurate, complete, and verifiable from source documents. In the current scenario a large number of sites are selected in a single country for a single protocol to meet the targets of the sample size. The requirements of the regulatory authority to prove the hypothesis on large number of subjects have resulted in multicentric trials. This has magnified the difficulties for the CRO’s in the conduct of monitoring and getting access to the site. Following are some of the problems associated with effective monitoring & site access.

Amount of data

The present multicentric scenario has resulted in large number of trial and also huge amount of data. Source document verification and finding of errors is main objective of monitoring. Such large amount of source data and documents along with CRF is bound to compromise the quality of effective monitoring. This will in turn hamper the data quality and timely completion of the trial.
Number of sites

With increase in number of sites throughout the country will also increase in the amount of traveling. The extent and nature of monitoring depend on the objective, purpose, design, complexity, blinding, size and endpoints of the trial. Generally onsite monitoring is done before, during and after the trial. The monitor is on the run always to cater to a large number of sites in providing protocol training as well as checking the compliance. This has been proved to be a hindrance in the effective monitoring.

Experience

The act of monitoring requires both qualification and most importantly experience. An experienced monitor can be a good communicator between the sponsor and the site. It also plays a central role in the quality of effective monitoring which is document verification and providing guidance to the site coordinators throughout the study period for a smooth conduct of the trial. But owing to the number of sites the ratio of monitor to site is inadequate. In India there is a huge deficiency of experienced monitors looking at the number of trails happening.

Responsiveness of the site

The access to a site is crucial in performing monitoring. The cooperation of the investigator and the coordinator from the site is required for monitoring. The site should be willing to accommodate the required number of monitoring visits. The coordinator should more often provide positive response to the monitoring intimidation letter to the site by the monitor. The investigator should be available during monitoring to discuss the relevant issues. Non availability of the investigator and packed monitoring schedule of the site are some of the deterrents in the conduct of effective monitoring in countries like India.

Solutions

The CRO’s need to improve the monitor to site ratio for the multicentric trials. The number of sites assigned to a monitor should not exceed the limit and hamper effective monitoring. CRO’s should organize training for the clinical research associates so that the skills can be developed as a monitor and also improve the vast requirement of trained and experience monitors. Performing a good site selection is vital for the success of the study. The CRA should assess the site for availability of space to conduct monitoring, agreement on the number of visits to be conducted and availability of the site personnel during the visits.
B. Data compilation, analysis & Storage

Data compilation is the process of gathering and measuring information on variables of interest, in an established systematic fashion that enables one to answer stated research questions, test hypotheses, and evaluate outcomes. While methods vary in the present scenario with options available for the pharmaceutical, biotechnology and medical device companies. They can opt for a paper mode of data collection or electronic data capture. Even there is the use of PDA as a patient reported outcomes or the use of IVRS. The selection will depend on the region of conduct of clinical trials, type of patients targeted, infrastructure etc. This area of global clinical trial has been proved to be a challenge which needs to be tackled with utmost importance.

The importance of ensuring accurate and appropriate data collection Irrespective of the field of study or choice for defining data, accurate data collection is cardinal to maintaining the integrity of research. Both the selection of appropriate data collection instruments (existing, modified, or newly developed) and clearly delineated instructions for their correct use reduce the possibility of errors occurring.

Aftermath resulted from improperly collected data include

- Incompetent to answer research questions accurately
- Inept to repeat and validate the study
- Misinterpreted findings resulting in wasted resources
- Deceive other researchers to pursue ineffectual avenues of investigation
- Compromising decisions for public policy
- Causing harm to human participants and animal subjects

The chief reason behind preserving data integrity is to reinforce the detection of errors in the data collection process, whether they are made willfully (conscious falsifications) or not (systematic or random errors).

The most evident of the causes which has transformed data collection in clinical trials as a challenge includes:

- Ambiguity about the timing, methods, and identify of person(s) responsible for reviewing data
- Partial listing of items to be collected
• Vague description of data collection instruments to be used in lieu of rigorous step-by-step instructions on administering tests

• Failure to identify specific content and strategies for training or retraining staff members responsible for data collection

• Unclear instructions for using, making adjustments to, and calibrating data collection equipment (if appropriate)

• No identified mechanism to document changes in procedures that may evolve over the course of the investigation.

Apart from the challenges mentioned above, the accuracy and credibility of the data collected is also hampered due to the following reasons:

• Flaws in individual data items

• Systematic errors

• Protocol violations

• Trouble with individual staff and site performance

• Scientific misconduct

• Willful deception by fabrication and falsification

Recommendations

1. Standardization of protocols.

2. Adequate validation mechanism in the data collected.

3. Protocol training

4. Training in using the data collection instruments

5. Active monitoring of the sites.

Data Analysis

It is the process of systematically applying statistical and/or logical capability to describe and personify, summarize and recap, and evaluate data. A crucial element of ensuring data integrity is the accurate and pertinent analysis of research findings. Improper statistical
analyses distort scientific findings, deceive readers and may negatively influence the public perception of research.

A dominant problem in the analysis of clinical trials is missing data induced by patients dropping out of the study before completion. This problem can result in biased treatment comparisons and also impact the overall statistical power of the study. The issue of missing data is often not a major concern until it is time for data collection. The rate of patient dropout is increasing in Indian sites. Many of them have been due to lost to follow up and poor effort by the sites in retaining patients.

Handling of missing data

1. Report reasons for dropouts and proportions for each treatment group
2. Conduct sensitivity analyses to encompass different scenarios of assumptions and discuss consistency or discrepancy among them
3. Focus in minimizing the chance of dropouts at the design stage and during trial monitoring
4. Collect post-dropout data on the primary endpoints
5. Consider the dropout event itself an important endpoint in studies with many cases
6. Sponsors should select sites with a good record of patient retention.

Data Storage

The storage of data has become increasingly challenging due to the amount of data produced. Some of the issues include the need for complex-data modeling features, advanced temporal support, advanced classification structures, continuously valued data, dimensionally reduced data, and the integration of very complex data. Collecting, storing and curating the vast quantities of scientific data in existence are not just important for regulatory submissions, but is also vital for ongoing pharmaceutical research and clinical trials. Serious commitment and investment is required by institutions to ensure that clinical and scientific data is stored.

CDISC is encouraging research firms to ensure that they build the correct data collection and storage systems into their projects from the start, by incorporating the concept into the initial planning stage. Use of data warehousing and data mining tools should be considered.
5. Site Accessibility

A site faces a lot challenge in various aspects of a clinical trial. Even though a site selection visits aim to objectively and rationally uncover the strengths and weaknesses of the existing business or proposed venture, opportunities and threats as presented by the environment, the resources required to carry through, and ultimately the prospects for success, hurdles remain in the path of a global clinical trial. Few of the points are discussed below in this context.

A. Subject Recruitment & Retention

Patient recruitment and retention in clinical trials is widely recognized as the leading bottleneck in drug development, and it is likely to remain an area of heightened concern for the next five years. Patient recruitment is crucial for the success of any clinical trial. Complete identification of eligible patients ensures both timely execution of the trial and avoids selection bias. Recruitment is a common and relevant issue in clinical trials. A recent analysis of more than 100 trials showed that less than a third of the trials achieved their original recruitment target and half were awarded an extension. The wide range of available trials and the heavy workload of physicians might limit the capacity to identify trials that are relevant for the patient. The delays in patient recruitment for clinical trials account for an average of 4.6 months lost per trial.

Surveys have shown a trend toward poor volunteer retention in studies, because overall one out of every four sticks with a study until its completion. Most participants dropout during phases II and III. (Center Watch, 2005). There are various factors which causes delay in patient recruitment which in turn causes delay in the development process for the sponsors. Even after getting recruited, the dropout rate for the patient’s is very high. This issue has to be tackled with foremost priority otherwise India may lose its advantage of being the clinical research hub of the world thus there will be a revenue loss for the country.

Challenges in Patient Recruitment & Retention

- Constricted eligibility criteria used to screen volunteers.
- Disarrangement of patient databases, and over or under estimation of patient recruitment rates.
- Patient awareness of the importance and need to conduct and participate in a clinical trial.
- Society's attitude towards a clinical trial.
• Non inclusion of media during the recruitment process socially hampering the recruitment and retention of patients in trials.

• Lack of adequate amount of interaction between the investigator and the patient.

• Shortage of databases of patient profiles, to assess whether they can be included in clinical trials.

• Busy investigators in a given therapeutic area as they may be working on multiple studies.

• Lack of communication skills of research professionals who are concerned with patient recruitment.

A majority of the Indian Patient’s have the following outlook towards Clinical Trial

• Unawareness of clinical trials.

• Not having adequate access to trial sites.

• Possession of fear, distrust, or suspicions of research.

• Practical or personal obstacles like family issues, lack of time.

• Doubt having to pay for the trial or not having adequate medical insurance.

• Not willing to go against family physician’s opinion.

• Unable to understand language and illiteracy rates may make it difficult for some people to understand and consider participating.

Solutions

• Development of open communication between the health care providers, clinical trial sponsors, media and public to ensure better patient recruitment and retention. This is crucial for the promotion of the importance of research in our country.

• Design of a trial should be well planned and correctly implemented. The subject’s recruitment strategies should be efficient to facilitate enrollment of patients into a trial.

• Sending the correct message across to the eligible subject is important for the recruitment process. Providing a good customer care service approach will beneficial
for the site. It is important to show that researchers care for the subjects. Respecting subject’s point of view is important in retaining patients in a study.

- Increase the patient’s access to the investigator, answering their queries and doubts throughout the study.

- Realistic sample size should be incorporated in a study because only a small fraction of potential subjects go through the screening phase, few of them get randomized and of which not all of the randomized participants complete the study.

- Comprehensive protocols, plans and strategies are required to address known barriers to facilitate and accelerate enrolment of underrepresented populations.

- Cultural and social factors, patient’s medical profile, emotional values, family support must be valued.

b. Ethical violation

A major concern is the ethical overlook of research involving human subjects in developing countries like India. Radical discrepancies in education, economic and social standing, and health care systems may endanger the rights of research participants. There may be a associated lack of knowledge of both the investigational nature of therapeutic products and the use of placebo groups. In some places, financial compensation for research participation may go beyond participant’s annual wages, and participation in a clinical trial may provide the only access to care for persons with the condition under study. The norm of health care in developing countries may also allow ethically disputable study designs or trials that would not be allowed in wealthier countries.

In one study, only 56% of the 670 researchers surveyed in developing countries reported that their research had been reviewed by a local institutional review board or health ministry. In another study, 90% of published clinical trials conducted in China in 2004 did not report ethical review of the protocol and only 18% adequately discussed informed consent.

Third world diseases

Clinical research should be compassionate to the health demands and priorities of the communities in which the research is conducted. With the rising global prevalence of conditions such as cardiovascular disease, it will be important to test drugs and devices on a global scenario. But among the ongoing phase 3 clinical trials that was examined that were sponsored by U.S. based companies in developing countries like India, none were trials of diseases such as tuberculosis that immensely affect the population of these countries.
Compassionate Use

Developing countries will also not recognize the blessings of trials if the drugs being evaluated do not become readily available there once they have been approved. The Declaration of Helsinki conveys an expectation that every patient enrolled in a clinical trial should, at the end of the trial, be reassured access to the best proven therapy identified in the study. The actuality is that the overwhelming majority of drugs for the treatment of common diseases are sold in the developed countries. Therefore, we need to confirm whether the growth in clinical trials worldwide is accompanied by greater availability of drugs in the countries where the trials are conducted.

Ethics Committee

The ethics committees can be defined as a board, committee or group formally designated by an institution to review, approve the initiation of and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. During the evaluation of the ethics committees of the developed and the emerging markets it has been found that the review boards or committees of Asia are weak in their functions compared to the established markets. India is not an exception. Some of the features which are found to be of concern during the documentation reviews and board observation includes

- Weak lay participation in IRB deliberations (board observation)
- Incomplete SOPs and inadequate SOP compliance (document review)
- Poor documentation and archiving procedures (document review)
- Incomplete review of ethical issues (document review and board observation)
  - Inclusion/ exclusion criteria
  - Vulnerability
  - Risk benefit assessment
  - Complete information in consent form
- Incomplete review of study design (document review and board observation)
- Inadequate documentation of IRB procedures (document review)
  - Incomplete minutes, incomplete protocol files
- Inadequate implementation of post review procedures (SAE reporting, progress and end of study reports)
- Unclear expedited review procedures.
- There are only a few ethics committees which hold meetings at regular intervals of the month for the review process. Takes a long time for approval thus delaying the start of study for the sponsors.

- Only some of the Ethics Committees are expert in providing opinions for sensitive issues like HIV trials with the stigma associated with it.

Informed Consent

This has been the most important topic of discussion form the times ethics evolved in medical research involving humans. Though in theory a lot of principles have been put forward in obtaining informed consent like giving complete study information, answering the questions of the participants, making them understand about the nature of the study and providing them ample time to make their choice. But in reality only few of the researchers would go through this pain. There have been reports of a large number of ethical violations happening in India with many studies conducted with no proper documentation of informed consent.

C. Reimbursement concerns

A critical issue that surface in the management of risk in clinical trials is that of compensation for the injury caused to the research subjects. There are contradicting opinions on the issue of compensation to research participants. Some researchers are of the opinion that Sponsors and Institutions should compensate injured research subjects, particularly in trials with commercial Sponsors, regardless of who may be to blame or whether the participants were reimbursed for participating in the trial. The other view is that periodic compensation is not required as subjects have been made aware of the risks through the informed consent process and have voluntarily agreed to participate in the trial. There are also empirical issues such as difficulty in figuring out whether a medical problem is related to the study medication or procedure, particularly if the injury develops months or years later or if the subject has other risk factors.

Most of the sponsors always consider a yearly insurance for all clinical trials conducted by them in that particular year and the amount for each trial was considered depending on the phase of the study, liability and the number of patients. Reimbursement of medical expenses is usually done directly in case of trial related injuries, especially in case of death, as insurance companies provided compensation only after comprehensively analyzing the circumstances surrounding the injury. A lot of time is wasted in this process.

Another concern is the variability in the amount of compensation from country to country by the sponsors, with India receiving the least as compared to developed countries. Sponsors defended their stance by hinting on the difference in the standard of living among the countries. Similarly the explanation given for statements mentioned in the informed consent form on compensation, for example, “compensation will be given only if the patient is not covered by his medical insurance policy” was that in countries like the USA, the subject’s
personal medical insurance pays for all expenses. Since these studies were global studies, the terms are kept constant.

It was rather discouraging to find out that about 33% of the informed consent document had in 2007 the proclamation that compensation would be given only after it was confirmed that the injury was due to the trial drug or procedure and if the medical care of the adverse event was not covered by the subject’s own or hospital’s insurance policy. None of the informed consent document mentioned compensation for lost wage, disability and discomfort in case of a research related injury. Moreover none of the informed consent document mentioned anything about compensation in case of death or long term injury. The situation has not improved much in recent years.

An important aspect that needs to be highlighted is the variability in the informed consent documents regarding the issue of financial cover for managing research related injury. There is no consistency in the language and the type of compensation offered. Some companies provided an Insurance cover to patients; some offered medical care only if not already provided by patient’s medical insurance while still others mentioned doubtful statements like “Compensation for injury will be in accordance with national and international terms and guidelines”. Some of the documents stated that compensation will be provided in accordance with Indian law. A few of them mentioned that payment of medical expenses could be obtained from the Study director. There was no clear information provided as to what was the compensation plan for the subjects by the sponsors. Even though insurance is considered for covering up of all the trial related adversities by the government of our country and the ethical guidelines but only a few of the studies provide such a support for the subjects as a way of reimbursement.

In India only sponsors have definite policies regarding compensation of patients in case of research related injuries and no such objectives by the institutions. It is also seen that the compensation was restricted to administering adverse events that occurred during a trial. The matter of compensation for lost wages during the adverse event, or for death, permanent disability or long term incapacitation is not labeled. Only some of the CRO’s or institutes are experienced in carrying out duties in the financial management of adverse events in India with no proper guidelines. One more culture that prevails in India is that most of the patient had to pay for adverse event management and will only be reimbursed later by the sponsors.

Below mentioned are some of the findings from a report published in 2007 which was prepared in association with WHO and CDSCO:

- Awareness about current Indian guidelines related to this issue was inadequate among the stakeholders, particularly investigators. As recommended by the ICMR guidelines (2006), no organization has an Arbitration Committee to address issues related to compensation amounts and mostly only Sponsors had formal legal advice for compensation issues.
- An interesting observation was related to the fact that most sponsors kept aside 5-10% trial budget for management of adverse events. Very few investigators and ethics committees did the same.

- There is very little experience in the case of fraud or negligence leading to adverse events and all stakeholders appeared generally unsure, although sponsors in general appeared to be keen on accepting responsibility.

- Although primarily responsible to review and approve, it was disconcerting to note that 83% of EC members were unaware of the details of insurance contracts. Most of the insurance was either product liability or clinical trial specific annual contracts. There is a large knowledge gap here that needs to be addressed, as well as a need to create information about the participants’ rights.

- The general lack of awareness among investigators regarding the issue of compensation for research related injuries. Although EC members felt the need to review compensation plans and documents, what was interesting was that they attributed this to a lack of time and expertise.

Two important highlights were that the “onus of proof” should not be on the patient or his relatives and the extent of compensation could decide on lines of “Workmen’s Compensation Act.” A point that needs to be discussed at length is the difference between countries on the “amounts” provided in insurance covers. The issue of “categorization” of injuries and defining compensation terms for these is another relevant key finding that needs to be discussed. The compensation is in the form of “reimbursement” and is often related to proving “causality”. Here too, it is clear that there are no plans to compensate in case of death or disability. Lack of uniformity in the language and the type of compensation offered are the hallmarks that must be changed.

D. Scientific impediments

There is a lot of concern in the scientific department of a global clinical trial regarding the validity of the results based on the trials done in a developing country like India and also on investigator requirements for conducting a trial. Here are some of the points discussed in light of the above issue.

Validity of results

The issue of concern is the validity of the projection of results for the entire world when trials are conducted in developing countries like India where there is a difference in the genetic composition, social consideration and the medical practice. Geographically distinct populations can have different genetic profiles, and these differences have been shown to be related to the safety and effectiveness of drugs and even medical devices. The food, culture and society play a very important role in how a drug behaves in the body. Though there are
provisions for different post marketing surveillances in countries regarding the safety issues but the initial clinical trials is the basis on which a marketing application is approved. Concurrent use of ayurvedic and home remedies might hamper the results. Even though there are a lot of precautions taken while conducting trials regarding these issues, but they cannot be completely avoided.

**Medical Practice and availability of drugs**

There is immense faith among the people with regards to their doctors in India. As it has been proved that the doctor-patient relationship has an influence on the drug action, this can be brought in light for clinical trials also. The patient reported outcome which is one of the important modes of data collection can be influenced because of such an attitude of the subjects. Another important concern is the over the counter availability of drugs. There are always only few drugs allowed as concomitant medications for subjects of clinical trial. But as in India drugs are for sale without prescription, subjects have access to any drug according to their will.

**Indian Investigators**

India is said to have a large pool of qualified investigators for clinical trials. But it is seen that there are a few experienced investigators. There is lack of GCP trained and qualified investigators in India who could be responsible for safeguarding the rights and safety of the subjects. One more observation that has been made is the amount of time dedicated to a trial by the investigators, which is surprisingly less. This affects the quality of the conduct of trial with respect to reporting and supervising, ultimately the data produced. It is also seen that several of the experienced and qualified investigators are simultaneously conducting many trials at a time hence not doing justice to any of it.

**Subjects**

Along with a large pool of doctors, India also has the advantage of having a huge therapeutically naïve population. Subjects go through various examinations and receive medication free of cost. There is also provision for reimbursement after the visits in many trials. This is a lucrative offer for the underprivileged population of India. There have also been reports that many of such patients are involved with more than one trial at a time. This is a serious concern because the results of trials might be influenced by each other.

**Solution**

- Create formal training programs for clinical research and ethics for investigators in developing countries to expand their global clinical research leadership capacity and improve collaboration between academic investigators worldwide.
• Create a mechanism for tracking investigators who are formally trained to conduct clinical trials as well as those who have been prohibited from conducting such studies.

• Sponsors need to describe how trial populations match their intended markets for the drugs or medical devices being tested.

• Create target enrollment of patients according to geographic region on the basis of the intended use of the product, similar to FDA and NIH policies for target enrollment of women and minorities in clinical trials.

• Investigators should provide adequate knowledge to the subjects about the requirements of trial based on the concomitant medications and abstinence from any other form of medications during the trial period.

• Development of methods to identify subjects who are already undergoing trial medications. Fingerprinting of the volunteers should be routinely undertaken by companies in India to prevent people from enrolling in multiple trials.
6. Laboratory Hassles

In Clinical Research Testing Laboratory have a major impact in determining the drug safety and efficacy. In past Sponsors used Local Laboratory available in the vicinity of investigational Sites. This practice included many problems like use of different methodologies reference ranges and reporting units leading to differences in analytical quality among various participating Laboratories. Other than these there were differences in ways of analyzing data. All these factors hampered the data quality and the heterogeneous database so collected could not be used to draw accurate scientific conclusions.

To work out above mentioned complications and hindrances Central Laboratory concept came into picture. This improved the quality of Laboratory data collected and simplified over all study Logistics. It also reduced the study cost. The major challenges faced by Laboratories include the activities like, coordination of sample transport, data management and creation of reliable database in a format importable by Sponsor/ CRO.

Figure below summaries the challenges faced by a laboratory

As shown in the figure the challenges can be divided into analytical and non analytical. Challenges faced during and after sample processing are categorized as analytical challenges and other challenges are defined as non analytical challenges. Analytical Challenges are further sub defined as pre and post analytical. Similarly non analytical challenges are sub divided into the one related to Quality and other to Logistics.

A. Laboratory selection

For a Laboratory to participate in Clinical Trial it should have valid accreditation certificate from internationally accepted Standards like ISO or some other local accreditation Organization for the test to be performed. Lab should have written and approved SOP which
should be strictly implemented and regularly revised. Staff should be continuously trained. Good Quality control and Quality Assurance system should be in place to ensure the quality of Lab results produced.

The equipment used should be periodically maintained and calibrated; reagents used should be tested and valid. Based on the requirements mentioned, a laboratory selection procedure represents a challenge both for the local and central laboratories in clinical trials and a good site selection is required in which the documents proving the quality and standard of the laboratory reflected is reviewed.

B. Sample Handling and Consignment

It is the most common pre analytical challenge. The participating Laboratory needs to be analytically and technically sound to perform the test parameters as per study requirement. Well trained and skilled staff should be there to carry out various operations. Infrastructure in use should be updated and well maintained. Other than this proper documentation is required at each step from sample receiving till the sample gets discarded.

Sample identification system should be there which uniquely identifies the samples before it gets processed. Sample should be processed only if the controls have been processed and their results are in range.

Among post analytical factors following are of major concerns

- Reporting units
- Data management
- Sample Storage and discard

Central laboratory is required to produce customized reports in a study specific layout using the reporting units which can be easily interpreted by the investigators.

A validated laboratory data management system should be in place to generate clean and reliable database in a format importable by Sponsor/ CRO. Data should be stored in secure place with restricted access to it; DBMS should have features like track changes and security. Facility of maintaining secure data back up should be there to ensure accurate data recovery if required.

Appropriate facility should be there to store samples before and after processing.

Laboratory should have waste management policy to discard the sample appropriately without causing any potential harm to environment.
C. Logistic Management

Sample Shipment and tracking is the most crucial part of the logistic management. This is the most critical challenge faced by both the Laboratories and the investigator’s site and also puts a burden to the sponsor.

Proper coordination and management should be there from the laboratory and involved courier services to ensure that sample reaches the Laboratory in the viability period. The courier person has to ensure the sample gets picked from site as soon as it gets collected. If due to some unavoidable circumstances the sample has to be left at site then site person should be instructed to keep the sample at appropriate temperature conditions at their end.

If sample has to be shipped in frozen conditions then Laboratory/ courier person should ensure that ample dry ice is present at site at the time of sample pick up and also during the transit time from site to central laboratory.

Another major challenge faced by Central Lab is of Bulk Supplies Shipment and their Logistics. Central Lab has to maintain an updated record for the supplies it has dispatched to all participating sites. It has to ensure that site has sufficient supplies at their end and required supplies are dispatched in time. Other than this all the expired supplies at site have to be restored with fresh supplies.

Thus for smooth functioning of Clinical research Operations Central Laboratory plays a major role. Only a well equipped technically sound laboratory with a strong data management and logistics management system can meet such challenging requirements.
7. Reporting Adverse Events

Adverse events continue to perturb all health professionals and are now perceived as an important cause of hospital admissions, with a magnitude ranging from 0.9–7.9%. Several studies conducted in developed countries have justified the handout of Adverse Drug Reaction to mortality and morbidity. A meta-analysis of 39 prospective studies from hospitals in the United States indicated that ADRs ranked as the fourth to sixth leading cause of death. The Uppsala Monitoring Centre (UMC) in Sweden is maintaining the international database of ADR reports and currently about 4.7 million case reports are received from several nations (96 member countries). But it is estimated that only 6-10% of all ADRs are reported. Even the serious adverse events are under reported in all patient-care environments.

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can, therefore, be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Adverse drug reactions are noxious and unintended responses to a medicinal product. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

India is the world’s second most populated country with over one billion potential drug consumers. A study by carried out in a tertiary referral centre in South India showed that admissions due to ADRs accounted for 0.7% of total admissions and deaths due to ADRs accounted for 1.8% of total deaths. Although, India is participating in the UMC program, its contribution to the UMC database is very little, which is expected considering the lack of awareness of reporting concept among Indian health care professionals. This problem is essentially due to the absence of a robust ADR monitoring system and also lack of a reporting culture among health care workers.

With over 1 billion USD worth of clinical trials conducted in India, it is very important to focus the attention of the medical community on the importance of adverse drug reporting to ensure maximum benefits for Public Health and Safety.

Problems

1. Underreporting is still a big problem

2. Large numbers of poor quality reports
3. Not all reports meet requirements of WHO Uppsala Monitoring Centre.

**Recommendations:**

1. Create awareness about the importance of reporting AE among the health care professionals.

2. Establish collaboration with national institutions, associations, and NGOs.

3. Increase the number of ADR monitoring centres under the Pharmacovigilance programme of India taking into account the size and population of the country.

4. Enhance the use of the Vgiflow software provided by WHO-Uppsala Monitoring Centre.
8. Clinical Trial Registration

Clinical trials have shown to be an important means of benefiting patients, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. But the data and reports of various trials are often difficult to find and in some cases do not even exist as many trials are withdrawn or are not published due to antagonistic or ambiguous results. This penchant for availability of only selective information from the infinite clinical trials conducted is not appropriate with the practice of evidence-based medicine. Presently a universal need has been felt on the compulsion for transparency, accountability and accessibility on the account of restore public trust in clinical trial data. This would be attainable only if all clinical trials conducted are registered in a centralized clinical trials registry. Registration of trials will assure transparency, accountability and accessibility of clinical trials.

ClinicalTrials.gov

The ClinicalTrials.gov trial registry was launched more than a decade ago. Since that time, it has been growing in response to various policy initiatives. The registry now contains information on more than 100,000 clinical studies and has surfaced as a chief component of many public health policy actions directed at improving the clinical research enterprise. In 2008, a database for reporting summary results was added to the registry. Section 801 of the Food and Drug Administration Amendments Act lengthened the legal requisites for trial reporting at the registry. It was passed into law in the midst of concerns about ethical and scientific issues affecting the design, conduct, and reporting of clinical trials. This involved the suppression and selective reporting of results based on the interests of sponsors, anonymous modification of pre decided outcome measures, off shoring of clinical trials and failure to report relevant adverse events. Among other things, the law mandates the submission of summary results data for certain trials of drugs, biologics, and devices to ClinicalTrials.gov, whether the results are published or not.

Clinical Trials Registry- India

The Clinical Trials Registry- India (CTRI), hosted at the ICMR’s National Institute of Medical Statistics (NIMS), is a free and online public record system for registration of clinical trials being conducted in India that was launched on 20th July 2007. Initiated as a voluntary measure, since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General (India) (DCGI). Moreover, editors of Biomedical Journals of 11 major journals of India declared that only registered trials would be considered for publication.

All the sponsors or researcher who plans to conduct a trial involving human participants, of any intervention such as drugs, surgical procedures, preventive measures, lifestyle
modifications, devices, educational or behavioral treatment, rehabilitation strategies as well as trials being conducted in the purview of the Department of AYUSH is expected to register the trial in the CTRI before enrollment of the first participant. Trial registration involves public declaration and identification of trial investigators, sponsors, interventions, patient population etc before the enrollment of the first patient. Submission of Ethics approval and DCGI approval (if applicable) is essential for trial registration in the CTRI. Multi-country trials, where India is a participating country, which have been registered in an international registry, are also expected to be registered in the CTRI. In the CTRI, details of Indian investigators, trial sites, Indian target sample size and date of enrollment are captured. After a trial is registered, the sponsor or the researcher is expected to regularly update the trial status or other aspects as the case may be. After a trial is registered, all updates and changes will be recorded and available for public display.

While the mission of the CTRI is to encourage all clinical trials conducted in India to be prospectively registered before the enrollment of the first participant currently, trials where patient recruitment has started or even completed are also being registered. Post-marketing surveillance studies as well as BA/BE trials are also expected to be registered in the CTRI.

Issues related to Clinical Trial registries

- There are definitely trials that are not registered in ClinicalTrials.gov or any other publicly accessible registry.

- Meaningless entry, internal inconsistency, data mismatch, lack of apparent validity like data is not plausible on the basis of information are some of the problems associated with the provided information.

- Structure of tables and relevant group names and descriptions do not permit a reader to understand the overall trial design or do not accurately reflect the design.

- New registry and registration policies are being implemented in specific regions and countries around the world. The World Health Organization has established a search portal that includes data from ClinicalTrials.gov and 11 other registries, totaling more than 123,500 records as of November 23, 2010. However, overlapping scope and incompetent coordination internationally have contributed to the difficulty in determining the actual number of trials being conducted.

Solution

- Stricter implementation of the regulatory requirement of registering clinical trials in CTRI or ClinicalTrials.gov.

- Sites should not agree to participate in the trials not registered by the sponsors.
• Ethics committees should not approve of trials which are not registered.

• Linking of Indian clinical trials registry (CTRI) to the International Clinical Trials Registry Platform maintained by the WHO.

• Providing of guidelines by the registries on the amount and quality of data submission
9. Case Studies

There are some of the case studies to show the current scenario of global clinical trials and the emerging markets of the world. Few of the cases have been reported to present the positive and negative aspects of global clinical trials with respect to India.

A. Trends in Clinical Trials in Emerging Markets

A web survey conducted in May and June in 2011 reveals the scenario described below, in context to the trends in clinical trials in the Emerging markets of the world. The survey included 116 biopharmaceutical professionals who have begun or plan to begin conducting clinical trials in emerging markets. It provides an idea about the preferred locations around the world for the conduct of results.

ClinicalTrials.gov, a registry and results database of federally and privately supported clinical trials conducted in the United States and around the world, currently reports close to 110,000 trials listed with locations in 174 countries. As of July 2011, more than 2,200 studies are hosted in China; about another 2,200 are taking place in Taiwan; and just over 2,500 are underway in the Republic of Korea. India also is another emerging market with a significant representation of clinical trials, with 1,628 studies listed in the registry. In South America, Brazil and Argentina are the forerunners, with 2,339 and 1,176 studies in progress, respectively. In Europe, formerly Eastern countries such as Poland, the Czech Republic, Hungary and Romania are emerging sites, though nowhere near the numbers of trials taking place in some countries in the west. Poland, with some 2,300 studies, ahead of Sweden and Switzerland, for instance, significantly trails sites such as France, with its 6,571 studies or the U.K., with 5,623 studies underway.

Clinical trials are either uniformly distributed between mature and emerging markets or that to some extent more clinical trial are conducted in emerging markets than mature markets. The industry is taking various courses to facilitate more global clinical trials. Mostly acquiring local framework developing it up using their own assets, or engaging a contract research organization (CRO) to carry out services for site monitoring, data management and other clinical activities.

The drive certainly is advancing when it comes to conducting clinical trials outside the limits of the United States or Western Europe. Fifty-nine percent of respondents mainly sponsors of clinical trials indicated they already have begun conducting clinical trials in emerging markets, and the remaining 41 percent had plans to begin doing so in the next 2 years. Asia is a main target for 46 percent of the survey respondents.
B. Violations of Human Rights

Informed consent is an essential requirement of clinical trials, which denotes that the patient undergoing treatment as part of the study should be made aware of the trial being conducted, the drugs being administered on him and its possible side effects. But India, at several occasions witnessed gross violations of human rights and ethical values while conducting trials on volunteers enrolled in studies.

In 1999, without obtaining consent of the patients who were under treatment in the government-run Regional Cancer Centre in Trivandrum, an experimental drug tetracyclinyl nor-dihydro-guaiaretic acid was administered on them. Though there was an established treatment for their condition, they were not informed that they were taking part in an experiment or that they were being denied an established treatment.

Similarly, in 2002, the pharmaceutical giant Novo Nordisk conducted multi-centre phase III clinical trials of a diabetes drug even before receiving the results of animal studies. The study report found that the drug, ragaglitazar, caused urinary bladder tumors in rats; and this should have been known before the drug went for phase I trials. The trials were conducted on 650 people from North America, 200 from Latin America, 100 from Australia / New Zealand, 800 from the European Union, and 200 from non EU Europe; and 550 from Asia.

In 2003, Mumbai-based Sun Pharmaceutical Industries Ltd. launched a promotional-cum-research program by getting private doctors to prescribe the anti-cancer drug Letrozole to more than 400 women as a fertility drug for ovulation induction. The company then publicized the doctors' reports to other doctors as "research", using their network of medical representatives. The drug was prescribed despite the fact that it was known to be toxic to embryos.
C. Indian Pharmaceuticals get USFDA nod

Four Indian drug makers — Dr Reddy’s Laboratories Ltd, Sun Pharmaceutical Industries Ltd, Torrent Pharmaceuticals Ltd and Aurobindo Pharma Ltd — have received approval from the US Food and Drug Administration (USFDA) to launch a low-cost version of blood-thinning drug Plavix in the US. The drug is used to reduce the risk of heart attack and stroke.

Dr Reddy’s has also secured a 180-day marketing right for its generic version in 300 mg. The Hyderabad-based company may have to share its right with two other foreign companies, Teva Pharmaceutical Industries Ltd and Mylan Inc, which were also among the first to file for a right to launch the generic version of the drug.

The approval assumes significance, given the huge market size of the drug. Plavix is the world’s second-largest selling drug brand. Marketed by Sanofi-Aventis in 75 mg and 300 mg tablets, Plavix garnered sales worth $6.7 billion (around Rs 36,850 crore) in the US in the year ended March 31, 2012.

This gives the information about the strength of the pharmaceutical industry in India which has been proved to be a boost for the quality of clinical trials being conducted, data being generated for the FDA approval. Though some hurdles lies in the path of conducting global clinical trials with respect to the ethical issues in India, but this would further encourage sponsors around the world in outsourcing trials to India.

D. Active role of Indian Regulatory Authority

The DCGI has banned CRO Axis clinicals from conducting bio-availability and bio-equivalence studies at its facility in Hyderabad. This move was taken due to the evolving of a number of reports that the trial run by Axis had violated Schedule Y of Drugs and Cosmetics Act.

The allegation was that during the trial of an anticancer drug exemestanne conducted earlier in 2011, AXIS had administered the drug to a group of women in Piduguralla, Andhra Pradesh without obtaining consent.

This prompted the DCGI to carry out a two-day inspection at the facility during the time which uncovered a number of violations. The investigators also revealed a number of irregularities in the above said study with respect to subject recruitment process, informed consent process, independence of ethics committee its review and decision making process. The regulatory authority of India also said theta the decision was in favor of public interest to ensure the safety of their rights and welfare. They had also said that all the studies conducted in Andhra Pradesh would be inspected to ensure that all the studied conducted according to the applicable regulatory requirements of our country and the ethical guidelines.
In another incidence an audit of a clinical trial conducted at the Bhopal Memorial Hospital and Research Centre (BMHRC) for Quintiles Transnational Corp. shows people who had enrolled for a trial were not compensated for the expenses incurred to participate in it. Mint reported in August that the regulator had ordered an audit of a clinical trial conducted by Quintiles at BMHRC on behalf of US-based innovator firm Theravance Inc. The trial was for its pneumonia drug Vibativ (whose generic name is telavancin). Theravance and its contract clinical research organization (CRO) Quintiles completed the telavancin trial in India in June 2007 after having screened eight people, while only four completed the trial. During the one-year period of the trial, three deaths occurred.

A person enrolling for a clinical trial is considered a part of a study and is paid a compensation for expenses incurred in related travel and other costs. This is mandatory. BMHRC reportedly conducted clinical trials on victims of the Bhopal gas tragedy between 2004 and 2008. Seven such trials have come under the regulator’s lens. Following this, DCGI ordered an audit of the clinical trial at BMHRC, especially as the hospital was entrusted with treating victims of the gas tragedy and conducting research into preparations for such emergencies.

The above incident gives us the picture of the threat on the safety of the rights and wellbeing of the subjects which are at constant stake even with the establishment of regulatory requirements and ethical guidelines. It also provides us with an idea about the strive and action of the regulatory authorities in their effort to secure the safety of the research subjects.
10. SWOT Analysis of Globalization in Clinical Trials

Outsourcing clinical research to the emerging markets of the world is the current trend of the clinical trial market. This globalization will further evolve in the coming decade and countries like India and China will continue to flourish in the field of clinical trial.

After having discussed about several challenges in conducting global clinical trials from each stakeholder’s point of view, we would like to sum it up with a SWOT analysis of globalization in Clinical Trials.

**Strength**

- Diverse genetic pool and disease variation
- Numerous government funded and private medical and pharmaceutical institutions with state of art facilities
- Cost efficiency (up to 60%) in comparison to USA/ Europe
- Fast recruitment of large number of patients compared to the western counter part though it has its own concerns.
- Establishment of Clinical Trial Registry
- Revamped regulatory regime
- Resource pool of well-trained, qualified, English speaking manpower.

**Opportunities**

- Generate huge revenues for the countries where trials are conducted.
- Create job opportunities for a large number of life science graduates with development of CRO’s, SMO’s, Data Management organizations & Pharmacovigilence programmes.
- Motivates the regulatory authorities to progress in their current policies to be in line with that of the developed countries like US and Europe. Thus also creating conducive environment for gaining hold of the clinical trial market.
- Creates awareness about the importance of research & development in the upliftment of society.
- Potential of getting marketing approval in a country where trials are conducted.
Weaknesses

- Lack of adequate mechanisms to safeguard illiterate and vulnerable patients, prevent informed consent violations and ensure proper functioning of institutional ethics committees.
- Number of clinical research professionals who are GCP trained.
- Sites conducting large number of similar trials at the same time.
- Quality of data generated as a result of an outsourced trial.

Threats

- Inadequate intellectual property rights, data protection & exclusivity policies that differs with countries.
- Countries like India who is one of the largest developers of generic drugs.
- Inadequate inspection & monitoring visits to tackle the amount of misconduct & fraud happening in clinical trials
11. Recommendations

India is striving hard to overcome the regulatory hurdles which stand in the way of a fast clinical trial market growth. This will prove not only to be a lucrative site for western sponsors to conduct clinical trials but also would quite the critics who are not in favor of foreign trials being conducted in India as it will assure greater safeguarding of the rights, safety & wellbeing of the subjects. We have suggested some of the steps which would play a key role in such a build up.

Overcoming the Regulatory challenges

1. There should be a provision for a separate checklist of the documents that are required to be provided to the regulator authority to get approval for the conduct of clinical trial in Indian. This checklist should be published in the CDSCO’s website.

2. DCGI should simplify the procedures for issuing test licenses and published a guideline on its website.

3. Greater emphasis is required in the development of human resource and recruitment of personals at the DCGI office to eliminate the manpower crunch of the regulatory authority which would help in the competency to review protocols hence reduce the time required for approval.

4. There is a dearth of FDA trained inspectors to carry out clinical trail inspections in India. As DCGI has suggested conducting routine inspections, this want of trained inspectors should be fulfilled.

5. In order to undergo strategic improvements and to meet the global regulatory requirements, there should be bringing up of academic experts and involvement of the sponsor’s representatives.

6. Initiate greater collaboration between the regulatory body, industry & academia by conducting meetings to discuss important issues related to global clinical trials. This helps to develop transparency in the relationship between the industry and regulators.

7. There is a need to upgrade the curriculum of pharmacy along with clinical research so that the professionals are intellectually fortified.

8. Need to conduct of training programmes for the investigators.

9. Create consumer awareness about clinical trials and develop a positive public opinion.
10. Planning for a link of Indian clinical trials registry (CTRI) to the International Clinical Trials Registry Platform maintained by the WHO.

11. Ensuring penal provisions for fraud & misconduct in clinical research.

12. Consider allowing conduct of First in Human studies after appropriate review by the authority, thus making the reviewing authority competent.

13. Allow Phase 0 (micro dosing) studies and phase 1 studies in the country in controlled manner by the regulatory authority.

**Ethics committees**

1. Making it compulsory for all Ethics Committees (ECs) to be registered with the Drugs Controller General of India (DCGI) so that they function in accordance with the guidelines provided in Schedule Y

2. Well documented eligibility criteria for the review and approval from the local and central ethics committees.

3. Strengthening the role of the legal member of a committee to provide strong opinions over the clinical trial agreements and reimbursement issues.

4. Greater vigilance over the trials that have been approved about their progress

5. Capacity building for a competent review on the inclusion/exclusion criteria, vulnerability, risk benefit assessment and complete information in consent form.

6. Develop competence in providing opinions to issues elated to stem cell research, HIV etc.

**Compensation**

1. Need to develop and implement clear National Guidelines (keeping in mind the special needs of the Indian participant) with regard to compensation for research related injuries (for both management of adverse events as well for compensation in case of death, disability, long-term incapacitation or development of congenital anomalies) in consultation with all stakeholders involved in clinical research, legal counsel (in keeping with the requirements spelt out in Schedule Y, 2005 and ICMR guidelines of 2006). These guidelines need to clearly spell out the responsibilities of each stakeholder, including the role of the Ethics committee while approving trials or settling claims. Issues such as compensation to be given to research subjects in case of Government sponsored studies and clinical trials with herbal drugs where adverse events are not/least expected also need to be addressed. An important aspect of these Guidelines would be to categorize
potential injuries likely to be faced during clinical trials, including risk assessment of the injury.

2. The ICMR Guidelines mention that an Arbitration Committee can settle claims for Compensation which needs to be elaborated by answering questions like how much compensation is appropriate? Can the compensation be along the lines of the “Workman’s Compensation Act”?

3. There is also an urgent need for training and awareness workshops for all those involved in clinical research including research participants.

4. A workshop with insurance companies is needed to create in them awareness regarding the needs from a patient’s perspective: the participant takes the risk, but is covered by the sponsor with an insurance policy and the conditions are then approved by the Ethics committees. There are many areas of potential conflicts that these need to be addressed at a workshop.

Reference


4. Clinicaltrials.gov

5. Clinical Trial Registry India ctr.nic.in.

6. National Pharmacovigilence Program of India


8. www.fda.gov


10. Clinical Trials New Horizon –India Dr. Surinder Singh Drugs Controller General (India)

11. smartinvestor.business-standard.com

12. Centerwatch.com