India was considered as one of the hubs for conducting major global multinational clinical trials. It still has the potential to establish itself as a hub for global Clinical Trials (CTs). There are several reasons to it, including but not limited to—a large treatment naïve population with diversity in the gene pool with a range of illnesses, many easily accessible tertiary care hospitals, relatively lower cost of clinical trials compared to the western countries, high enrolment rates, good patient compliance/retention, ICH GCP trained healthcare professionals (HCPs), a generation of gifted young medical students, scientists and researchers who are eager to contribute valuably to the advancement of medical science, availability of trained man power and infrastructure and fairly accommodative regulatory environment at least until now.

However, the current scenario tells us a different story. The recent amendments to regulation, has contributed to a decline in the Indian Clinical Trial Industry. There are several challenges that the sponsor companies are facing which are diverting them to conduct their trials in countries like China and Taiwan as they are disillusioned with the uncertain regulatory environment here. As well, many companies are as well going for locations like US, European Union, Canada and Malaysia going by the expertise and speedy clearances, which will be cheaper in the long run. Recently few academic NIH trials were also put on hold by US NIH. This trend is a big dent to the Indian CT sector.

According to the research firm Frost and Sullivan, the CTs business in India is estimated to be worth around USD 500 million, which projects that it will grow to USD 1 billion by 2016. However, the industry experts have estimated a loss of USD 150-200 million in the past six months due to the changes in the regulations. We will have to wait to see if this is still achievable.

**Recent Amendments to Drug and Cosmetic Rules**

In India, Central Drugs Standard Control Organisation (CDSCO) (headed by Drug Controller General of India) is the primary authority and “Drugs and Cosmetics Act, 1940” (along with the rules framed there

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<th>122-DAB</th>
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<td>- Compensation in case of injury or death during CT.</td>
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<td>- Free medical management for injury occurring to CT subject.</td>
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<td>- Requirements for financial compensation to nominee(s) in case of death.</td>
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<td>- SAE reporting requirements for Sponsor, Investigator &amp; ECs etc.</td>
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<td>- Permission of CTs.</td>
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<td>- Approval of ECs before trial initiation.</td>
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<td>- Annual reports of CT status.</td>
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<td>- Inspection of trial site and personnel by CDSCO to check compliance with Schedule Y and GCPs etc.</td>
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<th>122-DD</th>
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<td>- Registration of ECs.</td>
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<td>- Requirements &amp; guidelines for EC registration including application, composition, maintenance of records etc.</td>
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Compensation should be limited to the injury or death of the subject, resulting directly or justifiably related to the participation of the subjects in the CTs and not for unrelated events or any injury.

under) is the principal legislation for the regulation of CTs. Schedule Y of the Drugs and Cosmetics Rules (DCR), 1945 provides Rules relating to CTs in India.

Since last few years, it was required on the part of the DCGI to formulate new regulations or modify the existing ones in order to streamline the CT process in India. Recently, in January 2013, DCGI amended the DCR 1945 to bring the following three amendments. Few examples of each amendment are provided as well:

These amendments have brought sudden change to the CT regulations. Many of these amendments were long overdue and were very much required however without too many lacunas and should have been done in consultation with the stakeholders especially while finalising the amendments (Public, Sponsors, CROs, Academia, Ethics Committees, Regulators and Ministry) to avoid the anguish that the CT industry is undergoing currently.

The amendment has brought in several good changes (EC/CRO registration, GCP Compliance and other related quality changes), as well as challenges. Bringing these amendments is laudable. However, the current regulation is leaning primarily to guard the safety of trial participants and to improve the much criticised with a justifiable reason, inefficiencies of several Clinical research players including CROs, investigators, ECs, regulators and sponsors in managing properly ethically compliant CT process.

Hence, revision of the regulation was very much needed and is much welcomed after years of well-documented ethical lapses in few cases, including informed consent issues, protocol violations, compensation issues by the sponsors among others. Although the DCGI has made an effort to bring some stringent regulations and to create a structure similar or stricter than few regulated countries, there still are many lacunas in these amendments.

Challenges/Gaps in the Recent Amendment(s)

The language of regulation itself is ambiguous at places and has loopholes, which needs to be clarified,
- Compensation for “any injury” or death during CTs due to failure of investigational product to provide the intended therapeutic effect and use of placebo in a placebo controlled trial.
- Medical coverage and compensation for any type of injury whether it is related or not is a major issue, and there is no clarity for how long and how much compensation need to be provided which will be decided by the regulatory authority and ECs on a case by case basis. If this compensation is not provided, this may lead to the company suspending/losing the license to conduct CT in India on a case-by-case basis. This is acting as a deterrent for many pharma MNCs.
- The investigator’s obligation to report any SAE with 24 hours of the occurrence of the event is practically impossible as such information might not be available in the mentioned time period.
- The sponsor needs to report any SAE of death to EC and expert committee within 10 days of occurrence, while it is 14 days as per international practice.
- 21 calendar day timeline for EC to provide opinion on SAE as well as financial compensations.
- The timelines for EC to examine the SAE of death and for DCGI to determine the cause of injury/death are 30 days and 90 days respectively, which looks arbitrary.
- The amendments again fail to address issue of variable timelines for CT approval leading to significant delays and lost trust for the sponsor companies.

Challenges of Conducting CTs in India in General

1) Ethical issues
a. Even though, India has the manpower, experienced HCPs and infrastructure to handle more CTs, ethical oversight is somewhat missing. International companies are losing trust in the Indian institutes, as there have been cases of unethical practices in the past.

b. Until now, the ECs were not required to register with the DCGI. This led to independent working of the ECs leading to in few cases frauds and manipulation of trial data.

c. Another important challenge lies with the protection of rights of the subjects in the CTs.

d. No transparency in informed consent processing.

e. Involvement of major sub group of vulnerable population (illiterates, Villagers with lack of awareness, pregnant women and children) in trials leading to in few cases exploitation of the subjects.

2) Quality Issues
a. GCP issues, documentation issues, data quality/data protection/data compromise and fraud issues.

b. Different quality standards for local/global trials/BA/BE studies.

c. “Laissez faire” attitude leading to taking lightly some of the key ethical steps in CTs including improper documentation.

3) Regulatory issues
a. Delays/Lack of CT approvals: could be mainly due to shortage of technical/trained staff.

b. Lack of standardisation and transparency in CT approvals/audits/inspections and reason for decisions.

4) Cultural issues
a. In India, the personal physician strongly influences patient decisions, as do family and friends, which could raise potential ethical issues with patient recruitment unless the process is transparent.
b. Informed consent needs to be in local language. This means translation needs to be performed in multiple languages.

5) Media
a. There has been lot of negative publicity of CTs in India by media sometimes with biased/inaccurate data on safety related to CTs, which has led to overall negativity/uncertainties in subjects, industry and government leading to development of laws, which are very restrictive rather than supportive.

6) Training/Mentoring
a. Lack of practical advanced GCP and CT training of HCPs including regular up gradation and or maintenance of certification is a major issue.
b. India has an extraordinary pool of bright, insightful young medical talent who are often given minimal guidance and mentorship, and even less financial support in their endeavors leading to waste of talent.

Overcoming the Challenges

It is the hope of the clinical trial industry stakeholders that the recent amendments to the regulations once lacunas are addressed should be able to address many of the following critical steps leading to solutions to protect the integrity of Indian CT industry leading to India back on as a global hub for global CTs.

The amended regulations are great even though very stringent in few aspects and were needed for Mandatory GCP compliance, mandatory AE reporting, EC/CRO/CT registration including mandatory compensation for the subjects. However, the ambiguity in the regulations has to be clarified soon, as these regulations look more patient/subject friendly and lesser sponsors friendly so that there is a balance in the regulation enabling researchers to conduct CTs in India with integrity as ethically conducted CTs are very much necessary for drug discovery and treatment of rare complex diseases in India or globally.

Compensation and safety reporting amendments specially need to be revisited. Compensation should be limited to the injury or death of the subject, which are resulting directly or justifiably related to the participation of the subjects in the CTs and it should not be for unrelated events or any injury. There should be clarity on the compensation amount to be reimbursed. It is important that medical treatment for trial related injury should be covered by the sponsors.

However, there should be more clarity on the amount of compensation to be given, for how long the medical treatment should be given, and industry also should be able to participate in this calculation along with DCGI and ECs. There is urgency in this matter, as we have already seen a decline in the number of CTs in India since last year and companies moving their base to other countries. Positive note is that, the Drug Technical Advisory Board (DTAB), in their recent meeting on May 16th, 2013, has proposed few changes to these amendments which are still under discussion. For example: including the words “In the case of CT related injury” in the compensation clause to bring clarity that only trial related death/injury needs to be compensated for. Although they have not commented on the amount of compensation to be provided, they have recommended that a qualifying clause may be added “in case there is no permanent injury, the quantum of compensation shall commensurate with the inconvenience, loss of wages, transportation”. The DTAB has recommended the removal of the compensation for the failure of the investigational drug for intended therapeutic effect as well; they have added the clause use of placebo in a placebo controlled trial “if the standard care is denied”.

As discussed earlier, the timelines for SAE reporting are also a major concern and needs to be revised. For example, modifying the timelines to meet the international standards: 14 days instead of 10 days for sponsors and investigators, 30 days (instead of 21) for ECs to report SAE, 60 days (instead of 30) Expert committee to examine SAE and 60 days (instead of 90) for the DCGI to determine the cause of injury and decide quantum of compensation.

These are few recommendations that the DTAB has provided during their meeting in May. This might help to streamline the timelines and reduce the ambiguity in the regulations. However, it needs to be noted that these are only recommendations at this stage and are not approved yet.

It is crucial to increase the technical staff with advanced industry training at the DCGI office as they are currently understaffed/undertrained which leads to delays in approval of CTs. Further training by international regulator exchange programs
as well as advanced training in clinical trial design, implementation, monitoring, data management, and quality assurance including funding the DCGI’s office might help to improve the consistency of approvals, reduce the time taken for approvals and thereby increase the trust factor of the MNCs in the Indian regulatory system.

Once this is concluded, providing more power to DCGI’s office to make the decisions might be useful. As well, planned setting up of technical and regulatory expert committee to support CT application filing, review and related activities should take a priority and be established soon to streamline these activities. Streamlining of, and improved cross-communication and cooperation between the other agencies involved in the CT process approvals will be useful.

ECs need to be linked to Institutes, should have appropriate representatives and ideally should be monitored centrally. Constant monitoring and accountability of the ECs as well is the key to ensure quality ethical operation. ECs should do proper monitoring of trials including the consenting aspects, ensuring the diversity of trial populations so as to avoid misuse of vulnerable population including recruitment of poor homogeneous rural communities.

CROs when not meeting ICH GCP quality and ethical standards should be removed. A barrier needs to be created between industry and CT investigators to ensure ethical conduct of research. CROs should conduct trials to the internationally recognised standards by conformance to CT protocol and independent monitoring. Independent research in private clinics without supervision should not be allowed. There should be transparency at all levels- sponsors, CROs, Investigators, Regulators and ECs. Sponsors should ensure registration of all CTs in the CTs registry. Sponsors should also communicate risks/benefits of the trials including safety issues related to the drug/device including trial related risks to all the subjects including vulnerable population. Investigators should be transparent about the treatment given, adverse events, relatedness to the trial activities etc. with the public and regulators. Informed consent process need to be highly transparent and it should be voluntary and documented properly.

Transparency by the regulators in the entire process of CT application review with the appropriate reasons for approval or rejection of the application, approval criteria will be very useful. Transparency on CT audit, its process will be useful to build confidence in integrity of the data coming out of India. Increase in the number of Government regulated and funded CT centres, new initiatives for funding translational science/medicine with high-quality training in clinical research management, basic science research and Quality assurance is very much needed. Industry exchange programs should be encouraged at all levels so that Biotech/ pharma/clinical trial experts from developed regulated regions should be allowed to come to India to train our CT community including for regulators vice versa to foster cross-country collaboration initiatives.

Clinical research professionals including medical doctors in India need to be appropriately trained on ethics from the beginning during medical school. They need to be educated on the impact of unethical research on the subject, their family, CT industry and the country eventually. There should, not only be ethics courses included in the curriculum from the beginning, but also, annual ethics certification for CRAs and investigators to keep them up to date with the current regulations, GCPs and ethical conduct of CTs. CME credit could be provided to attend these training at least once or twice a year. People should own up responsibilities and the attitude of “Laissez faire” or casual attitude towards consenting, ethical/quality trials process including documentation need to go. The standard of clinical trial should be high irrespective of to which market this drug will go and whether the trial is local or global. Same high ethical and quality ICH GCP standards should be maintained at all levels (Sponsors, Investigator, CROs, Regulators, Ethics committees)

Media holds a key responsibility in the process too and it is hence critical for the media to present the right accurate data and not biased data especially on the CT related activities, adverse events, deaths and injuries related to CTs as presented before in several instances. It is very important for the regulators, the industry and the Government to come together and plan the regulations that protect the interest of the public at all times but, still have regulations that are supportive to the industry leading to the economic growth of the country.

Conclusion

There is an urgent requirement for readdressing some of the amendments to continue protecting the interests of subjects as a priority however, simultaneously upholding scientific research and development that will be beneficial to society. It is critical that clinical research community at all levels diligently follow the laws that are in place, understand and apply the guidelines and create a transparent trusted environment so that integrity of the Indian CT industry is maintained. It is the hope of Indian CT fraternity that new and reformed regulations once amended further will be able to bring back Indian CT industry to the highest global ethical standards.

Insufficient training or mentoring of young scientific community on advanced practical CT activities including practical GCPs is a real loss to Indian scientific community, as India could easily become a centre of basic medical and clinical excellence with a true Evidence-based Integrative Medicine. At every level the sponsor, investigator, monitor, regulator, inspector, CRA, clinical coordinator, there should be a clear focus on integrity and quality for India’s CTs industry to grow. Years may still be required before further clarity if brought in to address the current lacuna in the regulation, quality and ethical standards to effect all transformations, but it is the hope that this year forwards will see a tremendous move forward towards that goal.

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