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Regulation of Drug and Clinical Trials in India

Why RIGHTS Matter

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1. Context

The profit compasses of all multi-national pharmaceuticals are suddenly pointing to India. After computer chips, BPOs, and softwares that propelled the country's transition from a development laggard to a rising economic power, it's time now to harvest another resource – human bodies. And in this case, the poorer and disease wracked they are, all the more better.

The human drug trial market in India is today reportedly worth USD 400 million¹. And it is growing at a compounded annual rate of 30%! Till 1990s most clinical research was carried out in academic medical centres, paid for by government money. However, globalization and its economic twin, liberalization changed the scenario dramatically. Commercial interests now rule and financial bottom-line override ethical and human rights concerns, with predictable results. According to official figures, more than 1500 Indians have died in the course of clinical trials since 2008; around 670 fatalities were reported in 2010 alone². Media attention on the same and the groundbreaking evidence-led advocacy work carried out by public interest organizations have certainly raised the visibility of the issue. Concomitant to these developments, a slew of technical arguments have been put forth that rightly and vociferously argues for tighter regulations and oversight.

Notwithstanding the technicalities surrounding the debate, there is a compelling need to revisit the issue of clinical / drug trials from a human rights perspective. The rest of this paper discusses some disquieting and highly worrying pointers emerging from a pioneering initiative of Jananeethi³ currently underway in Kerala that locates and analyzes corruption in clinical/drug trials. Given the fact that it is the most marginalized and vulnerable in society who are likely to be exposed to these anomalies, it is pertinent that we widen the ambit of the discussion from a mere 'client' perspective with a focus on service rights to a much more potent 'citizen' perspective focusing on fundamental rights and universally accepted human rights norms.

¹ Jason Overdorf (2011). India: deadly drug trials. Global Post, June 19 2011. Accessed at <http://www.globalpost.com/dispatch/news/regions/asia-pacific/india/110618/india-health-drug-trials>

² Ibid

³ Jananeethi (People's initiative for human rights) is a registered non government organization which aims at radical changes in society through promoting and advocating human rights and civil liberties. Field observations quoted in this paper are the results from a project initiated to combat corruption in clinical drug trials in Kerala funded by the Partnership for Transparency Fund, Washington DC.

2. Overriding Economic Interests

Why is suddenly India in the radar of the global pharma industries? A strange concoction of market advantage, lax regulation and human misery explains the surge. Let us start with economics. It is estimated that the price of bringing a new drug to market is, on average, \$1 billion. The bulk of that cost is devoted to human clinical trials — the most crucial and time-consuming phase of drug development. Faced with tight regulations at home and shrinking profits due to expiring drug patents, it is no wonder that MNCs are looking at countries like India as the crucible; by shifting to India, for instance drug companies can cut the cost of clinical testing by 60%. To understand the economics further, it is essential to comprehend the drug testing process:

Phase 0: This is a recent designation for exploratory, first-in-human trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug behaves in human subjects as was expected from preclinical studies.

Phase 1: This is the first stage of testing in human subjects. Normally, a small (20-100) group of healthy volunteers will be selected usually in a hospital setting where the volunteers can be closely watched and treated should there be any side effects. Phase 1 trials are designed to determine how the experimental drug works in humans. That is, how the drug is absorbed, metabolized, and excreted. Additionally, they seek to determine what types of side effects occur as the dosage levels (that is, the amount of drug) are increased, as well as to obtain early evidence on drug effectiveness.

Phase 2: At this stage, trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase 3: In a Phase III study, an experimental drug is tested in several hundred to several thousand patients with the disease/condition of interest. Most Phase III studies continue to be randomized. The large-scale testing provides the pharmaceutical company as well as the FDA with a more thorough understanding of the drug's effectiveness, benefits/risks, and range/severity of possible adverse side effects. Phase III studies typically last several years.

Till January 2005, clinical trials of new drugs developed outside India were permitted only with a “phase lag”. This implied that a phase 2 trial could be conducted in India only after phase 3 trials were completed elsewhere. Phase 1 trials of foreign drugs were not permitted, except for drugs of special relevance to India.

However, in January 2005, an amendment of Schedule Y of the Drugs and Cosmetics Rules did away with the phase lag in international clinical trials. There are no longer any restrictions on “concurrent phase” clinical trials in India. Phase 2 and phase 3 trials of drugs discovered abroad may now be conducted in India in the same phase and at the same time as they are conducted in other parts of the world. It is now reported that further changes are in the anvil to allow Phase 0 trials also to happen in India. This has literally opened the floodgates for the gold rush.

But alongside, India also offers other advantages. It’s large, diverse and poor population offers an astounding pool for research on diseases. India have 40 million asthmatic patients, about 34 million diabetic patients, 8-10 million people with HIV, 8 million epileptic patients, 3 million cancer patients, more than 2 million cardiac-related deaths, 1.5 million people with Alzheimer’s disease; 15% of the population is hypertensive, and 1% suffers from schizophrenia. Add to that its large pool of half a million trained English speaking doctors, 15,000 hospitals with over 700,000 beds and 220 accredited medical colleges. Not to forget the fact that the majority of the poor in India are “treatment naive”, implying having being subjected to very few medicines and hence an unusual clean testing ground for research. And if any further doubt remains, here’s the final reassurance: doctors are seldom sued in India. The India allure is captured by a statement from Quintiles, the World’s largest Contract Research Organization (CRO): “It is practically a paradise for conducting clinic trials”⁴.

3. The Regulatory Quagmire

Blinded by the economic potential of tapping into the outsourced drug testing market, there is very little attention focused on substantive issues like lack of regulation of private trials and the uneven application of requirements for informed consent and proper ethics review. Cases of rampant collusion and ineffective regulation are widely quoted. As a recent report cautions: “On the ground in India, it is impossible to find anyone running, monitoring or auditing clinical trials who is not in the payroll of the drug maker”⁵. Doctors are paid according to the number of patients they enrol; reliable estimates put the rate as high as US\$2000 per patient in some cases. It is no wonder then that doctors in large public hospitals take on extra work related to clinical trials despite long waiting lines of people.

Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. The Rules are enforced by the office of the Drugs Controller General of India (DCGI) who is also responsible for monitoring all clinical trials submitted to that office for approval. Rules as amended in January 2005 require that the clinical study report include a

⁴ Accessed at <http://www.eatg.org/eatg/Global-HIV-News/Pharma-Industry/Time-bomb-The-clinical-trial-gold-rush-in-India>

⁵ Accessed at <http://www.tampabay.com/news/business/article934677.ece>

statement that the trial was conducted according to the principles of the Declaration of Helsinki, Indian Good Clinical Practice guidelines, and the Indian Council of Medical Research's ethical guidelines for biomedical research on humans. A critical entity in the scheme of things is the Ethics Committee that should be mandatorily setup at the sites where the tests are done.

However, an ICMR survey conducted in 2005 found that only 40 of 179 institutional ethical committees follow the prescribed legal provisions and function as per various ethical guidelines⁶. That is indeed a poor track record given the immense power wielded by this critical monitor.

Compounding these disablers is the profile of extreme misery and vulnerability. Daily encounters with poverty and indignities often force the healthy and the sick to be "willing" participants for the trials. According to the ICMR's guidelines, "... payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enrol in research against their better judgment, which would then be treated as undue inducement". However, the reality is often more grim. This is why stricter regulation and enforcement is absolutely necessary to prevent our hospitals from morphing into human laboratories.

One silver lining in the cloud is the creation of the Clinical Trials Registry of India (CTRI) in July 2007. CTRI mandates compulsory registration of all clinical trials conducted in India before the enrolment of the first participant.

4. Putting 'Rights' Back into the Discourse

Amidst the technicalities surrounding the debate, there is a compelling need to revisit the issue from a human rights perspective. Jananeethi's position in this regard follows this line of argument and builds on to a pioneering initiative currently underway in Kerala that locates and analyzes corruption in clinical/drug trials. Given the fact that it is the most marginalized and vulnerable in society who are likely to be exposed to these anomalies, it is pertinent that we widen the ambit of the discussion from a mere 'patient' perspective with a focus on service rights to a much more potent citizen perspective focusing on fundamental rights. The 'patient perspective' is particularly relevant for the focus of this discourse on clinical/drug trial as the primary target group in India are sick poor patients rather than healthy volunteers.

It is important to reiterate that the concept of patient rights globally evolved keeping the 1948 Universal Declaration of Human Rights which recognizes "the inherent

⁶ Quoted in Sandhya Srinivasan (2009). Ethical concerns in clinical trials in India: an investigation, Centre for Studies in Ethics and Rights, Mumbai.

dignity” and the “equal and unalienable rights of all members of the human family” as the primary reference. Any discourse on patient rights should imbibe this larger and fundamental spirit of inalienable human rights. Also, “the Universal Declaration of Human Rights has been instrumental in enshrining the notion of human dignity in international law, providing a legal and moral grounding for improved standards of care on the basis of our basic responsibilities towards each other as members of the “human family”, and giving important guidance on critical social, legal and ethical issues”⁷.

Yet another critical dimension to consider is the distinction and also, the interconnectedness of social and individual rights. This again arises from the profiles of victimization that coincide with profiles of social marginalization. Evidential and anecdotal pointers reveal that individual vulnerabilities are often a corollary and extension of social vulnerabilities. In the west, these two are treated separately and the broader rubric of human rights is linked only to individual rights. However, in the existing milieu in India, these two are more often than not mutually reinforcing links.

Locating human rights principles and covenants in the domain of clinical/drug trials have repeatedly come up in historical and contemporary debates on this theme. In general, four international covenants/codes are evoked⁸:

1. **Nuremberg Code** (articulated in 1947 by U.S. judges): “The voluntary consent of the human subject is absolutely essential . . . [and includes] legal capacity . . . free power of choice . . . sufficient knowledge and comprehension of the [nature, duration, and purpose of the experiment] . . . to make an understanding and enlightened decision.”
2. **International Covenant on Civil and Political Rights** (international treaty became effective in 1976): “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”
3. **Declaration of Helsinki of the World Medical Association** (promulgated in 1964 and revised eight times since): “The physician should obtain the subject's freely-given informed consent, preferably in writing. . . . [But in clinical research] if the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to [an] independent committee.”
4. **International Ethical Guidelines for Biomedical Research Involving Human Subjects** (published in 1993, and since revised, by the Council for International Organizations of Medical Science): “The investigator must obtain the voluntary, informed consent of the prospective subject [or legally authorized representative]. . . . Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.”

⁷ Accessed at <http://www.who.int/genomics/public/patientrights/en/>

⁸ Annas, George J. (2009). ‘Globalized Clinical Trials and Informed Consent’, *New England Journal of Medicine*, 360:2050-2053.

5. Insights from a Fact Finding Exercise

In 2009, Jananeethi initiated a project to combat corruption in clinical drug trials in Kerala with the financial support from the Partnership for Transparency Fund. The project sought to identify human subjects who have undergone clinical drug trials to investigate about the process and the impacts. The methodology also pursued key informant interviews with medical professionals and other critical stakeholders in the clinical drug testing domain.

Several observations and findings emerged from this intervention that have a major bearing on framing a Rights based discourse on this subject. Salient points are discussed below:

1. Flaws in informed consent process

The existing national (ICMR) and international guidelines on clinical drug trials make it mandatory that participants should be recruited for trials only after securing their informed consent. Our findings reveal that none of the participants were informed that they are being recruited into a drug trial. Further, the details of drug trials, risks and possible side effects of the trials were not communicated to the participants. One of the strange justifications put forward by a principal investigator of a clinical drug trial was that “if everything is communicated to the patients as required, they (patients) won’t agree to participate in the trial”. He further elaborated that due to their low level of understanding in this area the patients will misinterpret the information and will hesitate to participate! The patients were not given the copy of the signed informed consent form thus depriving them of any documentary evidence to prove their participation in a given trial. It was also found that doctors are recruiting their own patients without any monitoring by an independent doctor who is supposed to check the conflict of interests involved in such cases.

2- Absence of insurance coverage and compensation to the participants

The existing guidelines require ensuring proper insurance coverage or adequate compensation scheme for the trial participants. However, our findings show that in reality there is no insurance coverage or a compensation package for the participants. Ironically (thought not surprisingly) insurance coverage is available only to the doctor who conducts the trial in order to meet any liability that may occur due to any serious adverse event during the conduct of clinical drug trial. It was also revealed that the poor patients are denied a compensation for their opportunity costs, including daily wages and travel expenses.

3- Denial of post trial benefits

Ethical clinical practices require that once the trial drug is found effective the trial participants of the drug trial are entitled to get that drug either freely or at a subsidized rate. But this beneficial clause is not observed by the persons responsible for the conduct of drug trials. During a key informant interview with a leading Oncologist in Kerala who conducts several drug trials, we posed a question as to why he conducts clinical drug trials. His answer to the question was that he was actually doing a service to his patients by recruiting them in to drug trials because many of them were from a poor background and hence not in a position to access available standard treatment for their ailment. However, he had no answer to our question as to whether the trial subjects were getting those drugs at concessional rate once the trial was successfully completed. Two issues are worth highlighting: One, once the drug hits the market these poor patients are not able to buy the same because of its exorbitant costs. Two, during the trial period most of the trials are done on *Placebo* method, hence seriously ill patients are denied of available standard treatment. So, ultimately these patients due to their poverty are becoming guinea pigs for giant pharmaceutical companies and their vulnerability is exploited in the name of service.

4- The huge question mark over the 'Ethics Committees'

Maintenance of ethical standards and best practices in clinical drug trials are the mandated functions of the Ethics Committees (Institutional Review Board). But our findings clearly show that the incumbent ethics committees are far from positioned to play its mandated roles. The reasons are manifold: Our various interactions and interviews with the Chairmen and members of ethics committees of government and private medical colleges and hospitals clearly exposes that most of the members are totally ignorant about their role and responsibilities as an important constituent of the ethics committees. Most private hospital managements act as a 'cartel' helping each other and defeating the very basic purpose of the ethics committees. Further, Committee meetings take place irregularly, and members other than doctors from the concerned hospital are not attending these meetings, hence the ethics committee's approval becomes a mere sham. Most of the members are in some way related to hospital managements and in many instances, close associates of the principal investigator. Out of many members we interviewed, only one reported getting some training in this field. This is in clear violation of the GCP Guidelines that require every member getting some basic training in the good clinical practices.

5- Lack of Transparency

One of the most disturbing findings is the deliberate and wilful denial of any information with regard to the drug trials. The area of drug trials remains totally opaque; not even the names of Ethics Committee Members are disclosed! Even queries

posted under the much touted Right to Information (RTI) Act failed to elicit any response. Interestingly enough, most of our requests were turned down by the authorities raising the 'patient confidentiality' clause. We honestly believe that the confidentiality clause, meant to protect the best interests of trial participants in reality is being grossly and deliberately misinterpreted and misused to work against the interests of participants and hence needs a substantive review.

6- Questionable role of the CROs

The emergence of a new entity, namely the Contract Research Organization (CRO) has caused much concern and alarm in the area of medical research. CROs are often reported to be the front organizations promoted by large pharmaceutical companies. Drug trials often take place based on a secret understanding between the agents of the CRO and the concerned chief investigator, with the hospital management being kept in the dark in many cases. Our findings also show that the trials are being conducted in fairly large laboratories and post graduate departments in colleges. Doctors practice drug trials in their private clinics too. Hospital managements and medical practitioners are offered huge incentives and remunerations for obliging for such trials. Unfortunately, with the advent of CROs drug trials have become a highly lucrative commercial enterprise, with scant respect or regard to the rights and entitlements of the subjects who often come from the margins of the society. For these reasons, we strongly advocate that the CROs should be banned forthwith from the drug trial process. Further, we demand that every drug trial should be based on a MoU signed by the research institution and the concerned pharmaceutical firm, the terms and conditions of which should be clearly spelled, and made available in the public domain and the stake holders are held liable to any possible adverse effects on the participant.

7- Placebo method

As per the existing national and international guidelines *placebo* based trial can be carried only when there is no available standard treatment for the disease. But the fact remains that most of the drug trials are done on placebo that results in the denial of available treatment.

The findings and observations discussed so far, however singular and illustrative they are, point to an urgent need to review and revise some of the critical legal and operational parameters governing clinical drug trials in India. We list some pertinent points below:

1. Emergent pointers clearly underscore the need for a specific legislation with stringent provisions to punish violators and to safe guard the rights of trial participants. From our findings, based on actual interviews with the members of

ethics committees and doctors who conduct clinical drug trials, it is obvious that at present the protection of the rights of patients/participants solely depends on the personal integrity and honesty of the doctor and his/her team who conduct drug trials.

2. The role of the State as a regulatory arm comes out weak against strong entrenched corporate interests. Governments are largely ignorant about the volume and nature of drug trials that are being conducted in a particular jurisdiction. So it is of paramount importance that a state level mechanism, distinct from the DCGI and ICMR, be created in order to have strong monitoring on drug trials that are being carried out in respective states.
3. The composition, selection and function of ethics committee need a thorough review and revamping in order to make this body more effective. They should monitor the trial and must be allowed to meet trial participants on a random basis to ensure there is no serious aberration in the protocols and processes. This will help verify the genuineness of the informed consent and also eliminate the chances of corruption in the process of recruitment. It must be ensured that members of the committee are independent and got sufficient training on GCP. The details of ethics committee members (name, address and contact numbers etc.) must be publicly exhibited in the hospitals, conducting clinical drug trials and the same has to be made available to each trial participant. The decision of the ethics committee whether approved or disapproved must be published along with the reasons for the same and the same has to be shared. It is also ideal to have a central authority (similar to an Ombudsman) to monitor the functioning of ethics committees. The name and contact details of ethics committees must also be given in CTRI Registry.
4. Every participant must given an identity card apart from the signed copy of the informed consent form with necessary details regarding drug trials. This will serve as a strong evidence of participation and will be useful for claiming insurance / compensation for any adverse effects and also to ensure the availability of post trial benefits to trial participants.
5. Insurance coverage to trial participants must be ensured before they are recruited in to a drug trial.
6. Review the confidentiality clause; it is high time to review the confidentiality clause that goes against the interests of trial participants. In the name of protecting the commercial and trade interests of the company the confidentiality clause makes everything related to drug trials secretive. So, in our view except in case of disease

like HIV and similar diseases which may invoke social stigmatization on patients the details of drug trials and patients must be made public.

7. The details of drug trials including the patient's details must be retained for a minimum period of five years. Because in many cases the principal investigator leaves the hospital after or in the middle the trial and the side effects of the trial may occur after the trial period. It is also necessary that the drug trial must be done by the doctor with the full knowledge of the hospital management so that even if the doctor leaves the hospital the management could be held responsible for the reparation of participant's rights. During our study it was found that the doctor conducted a drug trail even without the knowledge of hospital management and once it was exposed there was no record available in the hospital.
8. It is also necessary to have a contract or a memorandum of understanding between all the parties involved in the drug trial process i.e. between the pharmaceutical company, CRO if they are involved, the principal investigator and the hospital management. This will help to ensure better transparency and accountability in the conduct of clinical drug trials.
9. The use of placebo must be avoided except where there is no alternative treatment available for the disease in question.

6. Need for a Patient / Participant Charter or Bill of Rights

Building on to the above deliberations, some critical elements can be drawn up as integral to any attempt to draft a Charter or a Bill of Rights in relation to drug/clinical trials in India⁹.

1. INFORMED CONSENT

- 1.1 The informed consent of the participant/patient in the presence of a third party is a prerequisite for the conduct of any drug/clinical trial.
- 1.2 Such trials should not be carried out on those who are unable to express their will, unless the consent of a legal representative has been obtained and the trials would likely be in the interest of the patient/participant.

⁹ Some elements have been adopted from (a) A Declaration on the Promotion of Patient Rights in Europe, WHO 1994. (b) Patient Bill of Rights accessed at http://www.cc.nih.gov/participate/patientinfo/legal/bill_of_rights.shtml

- 1.3 A participant/patient has the right to refuse or to halt a medical intervention. The implications of refusing or halting such an intervention must be carefully explained to the patient.
- 1.4 In all other situations where the patient is unable to give informed consent and where there is no legal representative or representative designated by the patient for this purpose, appropriate measures should be taken to provide for a substitute decision making process, taking into account what is known and, to the greatest extent possible, what may be presumed about the wishes of the patient.
- 1.5 The participant/patient has a right to refuse to participate in research, to refuse treatment to the extent permitted by law, and to be informed of the medical consequences of these actions, including possible dismissal from the study and discharge from the health facility. If discharge would jeopardize their health, they have the right to remain in the medical facility until discharge or transfer is medically advisable.

2. CONFIDENTIALITY & PRIVACY

- 2.1 All information about a patient's health status, medical condition, diagnosis, prognosis and treatment and all other information of a personal kind must be kept confidential.
- 2.2 Confidential information can only be disclosed if the patient gives explicit consent or if the law expressly provides for this.
- 2.3 All identifiable data must be protected. The protection of the data must be appropriate to the manner of their storage. Human substances from which identifiable data can be derived must be likewise protected.
- 2.4 Patients/participants have the right of access to their medical files and technical records and to any other files and records pertaining to their diagnosis, treatment and care and to receive a copy of their own files and records or parts thereof.
- 2.5 Patients/participants have the right to demand the correction, completion, deletion, clarification and/or updating of personal and medical data concerning them which are inaccurate, incomplete, ambiguous or outdated, or which are not relevant to the purposes of diagnosis, treatment and care.
- 2.6 There can be no intrusion into a participant's/patient's private and family life unless and only if, in addition to the participant/patient consenting to it, it can be justified as necessary to the participant's/patient's diagnosis, treatment and care.

2.7 Medical interventions may only be carried out when there is proper respect shown for the privacy of the individual. This means that a given intervention may be carried out only in the presence of those persons who are necessary for the intervention unless the patient consents or requests otherwise.

3. Service Entitlements

3.1 Patients/participants have the right to be treated with dignity while undergoing the drug/clinical trials and should be rendered with respect for their culture and values.

3.2 Patients/participants have a right to know the purposes and likely complications of any treatment procedures or investigations before they are performed, and whether there are any other alternatives.

3.3 Patients/participants have a right to avail insurance and/or compensation package in case of any adverse effects arising out of the trial.

3.4 Patients/participants have a right to be informed about the process of registering grievances, including designate authorities, timeframes, compensations (if any) and appeal mechanisms.

3.5 In case of a litigation, which is ruled in favour of the patient/participant, they will have a right to seek compensation from the facility to off-set all legal expenses and opportunity costs.

3.6 Patients/participants have a right to be informed about the composition, responsibilities and members of the Institutional Ethical Committees.

3.7 Patients/participants have a right to be informed about the market availability of the drug which has successfully passed the test phase and also, have a right to access the same free of cost or at a highly subsidized rate.

Blinded by the economic potential of tapping into the outsourced drug testing market, there is very little attention focused on substantive issues like lack of regulation of private trials and the uneven application of requirements for informed consent and proper ethics review. As a recent report cautions: "On the ground in India, it is impossible to find anyone running, monitoring or auditing clinical trials who is not in the payroll of the drug maker"¹⁰. Jananeethi believes that the unfettered growth of the clinical drug trial industry in India has all the portents of a Frankenstein creation and unless immediate steps are taken the future looks exceedingly grim for millions of those in the margins as they come in contact with a rapacious health care system.

¹⁰ Accessed at <http://www.tampabay.com/news/business/article934677.ece>