National Consultation on

Regulation of Drug Trials

26th - 27th September 2011, New Delhi

A report by

Sama - Resource Group for Women and Health
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Sama-Resource Group for Women and Health
B-45, 2nd Floor
Main Road Shivalik, Malviya Nagar
New Delhi- 110017
Ph. No.: 011-65637632, 26692730
E-mail: sama.womenshealth@gmail.com

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THE CONSULTATION IN PERSPECTIVE

There have been recent shifts in the trends of drug development, leading to an increase in the recruitment of participants, with India becoming an attractive destination for internationally, outsourced clinical trials.

An increasing number of pharmaceutical companies have started outsourcing drug trials to Contract Research Organisations (CROs) in developing countries; these now make up a specialised global industry that focuses on the research and recruitment of human subjects. India has a huge ‘treatment naive’ patient base, low cost advantage, ‘efficient’ conduction of trials, ‘improving’ infrastructure, and strong State support for outsourcing and privatisation. It is hence, witnessing an unprecedented growth in its drug trial markets. This market has grown from Rs 423 crore in 2005, to Rs 1611 crore in 2010, and is expected to cross Rs 2721 crore by 2012.

However, despite this phenomenal growth, there have been several controversies over the conduct of clinical trials in India. In the last few years, many drug trials have taken place without proper protocols and informed consent. At the levels of planning, design and implementation, there is a lack of transparency. Without adequate and necessary regulatory jurisdiction or systematic review, the reliability and validity of such research is jeopardised.

Currently, the infrastructure for regulation, ethics review and monitoring is insufficient to regulate clinical trials in the country. In this situation, the government’s push to encourage clinical trials in India must be viewed with concern. There is an urgent need for a policy that truly engages with and respects the public by according the highest priority to transparency in clinical trial procedures, as well as the protection of the rights of the participants. This is particularly critical in the context of medicine and vaccine trials, placebo-based trials, and genetic studies as these are often in violation of both, the Declaration of Helsinki as well as the guidelines for biomedical research by the Indian Council of Medical Research (ICMR).

India also requires a more stringent regulation, and effective implementation, in order to ensure the highest standards of independent inquiry, good clinical practice, enforcement of protocols, monitoring, and follow up, so that a strong and pro-people policy can be put into place.
Sama’s work in the context of medical research in India began with its engagement in the campaign against unethically tested and invasive hormonal contraceptives, and the anti-fertility vaccine. Sama members were also involved in the campaign against the violation of the rights of women participants in the Institute of Cytology and Preventive Oncology (ICPO)-ICMR\(^1\) natural history study on the progression of cervical cancer that came to light in the mid nineties. More recently, Sama has been actively involved in the campaign against unethical implementation of the Human Papillomavirus (HPV) vaccination ‘demonstration projects’ in India.

An effort was made to build on the learning and experiences of these campaigns and at the same time, to get a perspective of the broader arena of the clinical trials industry in India today. As a part of the campaign for regulation of drug trials, we needed to understand the existing gaps in policy and its implementation vis-à-vis regulation, towards developing an appropriate future framework in this regard. Recognising the urgent need for furthering transparency in trials, protection of participant rights, and implementation of the highest standards of independent inquiry, a National-level Consultation on the Regulation of Drug Trials was organised by Sama-Resource Group for Women and Health, during 26–27 September 2011 in Delhi, in collaboration with the Centre for Studies in Ethics and Rights (CSER); Low Cost Standard Therapeutics (LOCOST); All India People’s Science Network (AIPSN); Drug Action Forum, Karnataka (DAF-K); and Dr Amar Jesani\(^2\).

A preparatory meeting was held prior to the National Consultation in June 2011, when the organisers got together to define the objectives of the consultation and to deliberate the themes and presentations, to minimise repetitions and rhetoric, and to structure the consultation in a way so as to ensure concrete recommendations.

\(^1\) A study on the ‘Natural History of Pre-cancerous and early cancerous lesions of the uterine cervix’, was conducted by the Institute of Cytology and Preventive Oncology (ICPO) in collaboration with the ICMR, between 1976–1988.

\(^2\) Sama is a Delhi based resource group working on issues of women’s rights and health. Sama seeks to locate the concerns of women’s health in the context of socio-historical, economic and political realities.

Centre for Studies in Ethics and Rights (CSER) is a research and training institute of the Anusandhan Trust and one of the pioneering bioethics institutes in the country. It undertakes research and training to promote ethics, human rights and social relevance in the different aspects of public life.

LOCOST (Low Cost Standard Therapeutics) based in Baroda makes rational essential and quality medicines at affordable prices for those working with urban and rural poor in India.

All India People’s Science Network (AIPSN) is a network of organisations / constituents of the people’s science movement, working in various states with a social outlook, towards propagation of literacy and scientific temper among the masses.

Drug Action Forum - Karnataka (DAF-K) is a non-profit voluntary organisation that campaigns for a rational drug policy. It is a member of Health Action International Asia Pacific, All India Drug Action Network, and Jana Arogya Andolana – Karnataka.

Dr Amar Jesani is one of the founders of the Forum for Medical Ethics Society and its journal, IJME and was National Coordinator of the 2005 and 2007 IJME National Bioethics Conferences.
The National Consultation was attended by nearly 60 participants, who mainly comprised of representatives from health networks, the medical and scientific community, research organisations, media, activists, legal experts, women’s groups and policy makers towards evolving concrete recommendations for policy and regulation on these issues. The main objectives of the consultation were to:

(1) open the channels for dialogue and deliberation between science and policy, so that a framework for regulation could be developed.

(2) create a space for dialogue and discussion on policy-level advocacy, for the regulation of clinical trials in India, including ethical obligations and management of conflict of interest.

(3) develop an understanding of the multi-faceted nature of drug trials in India and explore its links with business and commerce, ethics and human rights; to analyse its relationship with a growing biotechnology and pharmaceutical industry.

(4) identify the gaps as well as strengthen the existing provisions for regulation such as Schedule Y of the Drugs and Cosmetics Act, and Ethical Guidelines for Biomedical Research on Human Participants by ICMR.

The first day of this two-day consultation provided the larger picture of the clinical research scenario and the related issues and concerns. Presentations and discussions focussed on the development and dilemmas pertaining to the new division of labour in commercialised research and the CRO industry; the regulatory provisions including ICMR’s Ethical Guidelines for Biomedical Research on Human Participants, the proposed bill on Human Subject Protection in Health Research and the review of Schedule Y of the Drugs and Cosmetics Act. Adverse events (AEs) in clinical trials and their assessment, management and issues related to compensation as well as the role of ethics committees (ECs) and other existing regulatory infrastructure for clinical trials in India, were also presented and deliberated upon.

The second day’s presentations and discussions were on public health and clinical trials; the concept of surplus health in the context of clinical trials and access to medicines, and issues related to governance based on experiences and examples of the recent indiscriminate conduct of clinical trials - the Human Papillomavirus (HPV) ‘demonstration project’ in Andhra Pradesh, clinical trials conducted at the MY Hospital, Indore, the Bhopal Memorial Hospital and Research Centre and in Ahmedabad, etc.

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3 HPV Vaccine ‘Demonstration Project’ was conducted in Andhra Pradesh and Gujarat by PATH International with the ICMR and the respective state governments.
The concluding session provided an opportunity to strategise for future actions towards people-centric clinical research. During this session, the participants collectively drafted a list of recommendations based on the discussions over the two days. A press brief based on the recommendations was disseminated to the media representatives who were invited to this session.

The structure of the report follows closely from the Consultation. All the sessions have been arranged in the order of them being conducted over the two days. The presentations and the following discussions in each session, have been documented closely to the actual proceedings, mostly verbatim, to maintain the authenticity of the content. The central concerns and points that were discussed have been highlighted at the end of each session.
The Current Scenario

Discussant: Dr Samiran Nundy, Head of the GI Surgical Department, Sir Ganga Ram Hospital

Chairs: Ms Brinda Karat, Ex MP of Rajya Sabha; Vice-President, All India Democratic Women’s Association (AIDWA)
Mr L.C.Goyal, Additional Secretary & Director General, CGHS, MoHFW

This session provided an overview of the clinical trial industry in India. The presentation by Ms Anjali Shenoi from Sama, mapped the scale and scope of the industry in India today. She traced the growth of this industry from a minor player to a global phenomenon and examined some of the main factors that contributed to this exceptional growth.

Ms Sandhya Srinivasan from the Indian Journal of Medical Ethics (IJME) highlighted some of the issues that this exponential growth of clinical trials has thrown up in the Indian context. The two presentations laid the ground for the main themes of the consultation that were deliberated upon over the two days.

Presentation I — Mapping the Contours of Clinical Trials in India: Context

Ms Anjali Shenoi

The Global Clinical Trial Industry

Over 60 per cent of the global pharmaceutical market share belongs to the United States of America (USA) based pharmaceutical industry, which impacts not just the research agendas, but also the type of drugs tested in clinical trials, the research that is published, and the drugs prescribed by the medical profession. The early nineties saw a shift in clinical trial sites from academic medical institutions to hospitals and private clinics, and from ‘traditional’ regions like the US and Western Europe to ‘non-traditional’ regions such as Eastern Europe, Africa and Latin America. Today, many of the new trials are conducted in geographical areas, where there is political and economic instability and unprecedented healthcare crises, and where participants are readily accessible. The US Food and Drug Administration (USFDA) has also made a concerted effort to promote the globalisation of clinical research operations. In 1996, the USFDA, in collaboration with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, developed guidelines to harmonise and unify Good Clinical Practices (GCP) of the European Union, Japan and the US in order to facilitate mutual acceptance of clinical data by regulatory authorities in their jurisdiction.
Participation of clinical investigators in US sponsored research increased dramatically as they were pursued by the pharmaceutical representatives in countries that had voluntarily agreed to harmonise standards in the field of commercial drug testing. These countries included Argentina, Brazil, Hungary, Mexico, Poland, Russia, and Thailand, amongst others. This also resulted in a sharp increase in the number of international human subjects involved in clinical trials outside of the US, from 4000 in 1995 to 400,000 in 1999. By 2004, about 42 per cent of the expenditure related to drug development in the US, was assigned to outsourcing, and by 2005, about 40 per cent of all clinical trials were carried out in ‘emerging markets’. However, it is important to note that while there has been a substantial increase in the outsourcing of trials, a study conducted in 2007 revealed that the US had the largest number of trial sites, followed by Germany.

**Main Push Factors - Why India?**

One of the main factors that contributed to outsourcing was, not surprisingly, the high costs of drug trials in the developed countries, the ‘tedious’ regulatory requirements of the FDA (time-consuming approvals, etc.), the need for a large number of research participants of varied ethnicities, a naïve patient pool who were not undergoing any treatment. This later became particularly relevant with the subsequent ban on research on prison populations in the United States.

India, with its genetically diverse population of more than one billion people, who have not been exposed to many medications, but have a myriad of diseases ranging from tropical infections to degenerative diseases, is being increasingly viewed as an attractive destination for clinical trials. Moreover, because of considerably low costs of trial per patient, infrastructure, and cheap labour, the total cost of conducting clinical trials in India is only 20 to 60 per cent of the cost in developed countries. Also, the enthusiastic investigators speak English, and there are a number of premier medical institutes in the country, which are comparable to those in developed countries. There is good patient compliance and retention, and most importantly, there is an ‘increasingly accommodating regulatory environment’.

In 2005, the Indian government actively started working towards becoming a favoured destination for global clinical trials. Further, the amendment to Schedule Y of the Drugs and Cosmetics Act significantly altered the nature and form of the clinical trial industry in India. As per this, concomitant Phase II and Phase III trials were allowed for drugs developed outside India, as opposed to the earlier prescribed phase lag to protect Indian participants from being the first to be exposed to the risk of the drug being tested. This not only facilitated the entry of global clinical trials in India but also expanded its scale. The industry witnessed a jump in the number of registered trials from 64 in 2006, to 425 in 2009.
Scale and Growth

Currently, close to 1506 trials are being conducted in India; the highest in the South Asia region, followed by Pakistan at 157 trials. In the Asia region, however, China is the market leader, with a total of 1975 trials.

The clinical research industry in India touched $258 million in 2008, up from $140 million in 2006, while the CRO market in India has grown from Rs 423 crore in 2005 to Rs 1611 crore in 2010 and is expected to cross Rs 2721 crore by 2012. It is estimated that by 2012, 5 per cent of the world’s clinical trials will be conducted in India. According to a Country Attractiveness Index for clinical trials in countries outside the US, developed by management consultants A.T. Kearney, India was rated second after China as the most sought after global destination for clinical trials. In fact India scored higher than the US on the Index in the context of patient availability. A look at the Clinical Trial Registry of India (CTRI) data reveals that a substantial number of Phase III trials are being carried out using foreign funding (164), as opposed to Phase III trials receiving funding from India (96).

However, it is pertinent to note that despite these figures, India still accounts for only 0.1 per cent of the total research and development (R&D) budget of the US pharmaceutical industry. This raises important questions regarding the actual enhancement of research capacities within the country.

Location and Growth

While the clinical trials industry has largely been concentrated in urban and semi-urban areas, its presence has been observed throughout the country, with certain areas emerging as prominent hubs. The Clinical Trials Watch, an initiative to track data registered on the CTRI has, as of 30 June 2010, recorded 1078 registered trials. The majority of these (666) are drug trials. The state of Maharashtra has recorded the highest number of trials at 531, followed by Karnataka at 321, Andhra Pradesh at 216, Gujarat at 210, Delhi at 141, and Tamil Nadu at 176. Within the States, the larger cities have recorded a higher density of trials, with Bangalore recording the highest number of trial sites at 215, followed by Pune at 189, Hyderabad at 180, Mumbai at 178, Delhi at 141 and Ahmedabad at 139. A few second rung cities such as Nasik, Nagpur, Mangalore, etc., have recorded over 50 trial sites.

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4 15 countries were analysed on the basis of patient pool, cost efficiency, relevant expertise, regulatory conditions, national infrastructure and environment.

**Nature of Trials**

Not surprisingly, diseases or conditions considered ‘lucrative’ are prioritised over diseases of ‘impoverishment’ such as tuberculosis (TB), malaria, etc. Analysis of the pharma-sponsored trials, as per the US registry for 2005-07, reveals a large number of trials in oncology, followed by trials on disorders of the central nervous system. Similarly, the data on CTRI shows the highest numbers of pharma-sponsored trials for various cancers (100), followed by diseases of the circulatory system (67), and endocrine, nutritional and metabolic diseases including diabetes, obesity and cardio-vascular disorders (63). A significant number of trials registered are pharmaceutical – placebo controlled Phase III trials.

**Multiplicity of Actors**

The clinical trials industry comprises multiple actors, with the pharmaceutical and biotech companies occupying top positions. Multinational drug companies and biotechnology firms are the main sponsors of clinical trials across the world. Data from the CTRI reveal that 456 trials, comprising 68 per cent of the total trials, were sponsored by pharmaceutical companies. Prior to 2006, there were only 29 pharmaceutical sponsors of clinical trials in India compared to 350 in 2009.

Following not far behind the pharmaceutical companies, is the burgeoning CRO industry. Contract research in the Indian pharmaceutical industry is already a robust sector, and was estimated by the Chemical Pharmaceutical Generic Association to be worth $100 to $120 million in 2005, and growing at 20 to 25 per cent per year. Currently, there are more than 150 CROs in India, out of which 20 claim that they are compliant with International Conference on Harmonisation (ICH) - Good Clinical Practice (GCP) guidelines. There are several multinational as well as local CROs, including big names like Quintiles, LAMBDA⁶, etc., whose motto is ‘time and speed’. Although they boast of an independent network of investigators and ethics committees, they are at present operating in a regulatory void.

Another subset in this category is the physicians who actually conduct the trials, even though in the Indian context, they have a relatively marginal presence compared to the CROs, in setting the infrastructural and regulatory agenda for research.

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⁶ Lambda Therapeutic Research Ltd is a leading Multinational CRO.
The State also plays a major role in the clinical trials industry, along with the international donors and funding agencies. However, the main regulatory authority in the country is the DCGI, and the premier research agency is the ICMR. The primary job of legislation is carried out via Schedule Y of the Drugs and Cosmetics Act. The amendments to Schedule Y have significantly changed the nature and form of the clinical trials industry, giving further impetus to numbers. Not surprisingly, these amendments were carried out in the same year that the country became compliant with the trade related aspects of intellectual property rights (TRIPS) agreement. The Ministry of Science and Technology is also actively involved through its Department of Biotechnology, which looks at clinical research as part of a wider initiative to make India a ‘global biotechnology power’.

Lastly, and unfortunately lowest on priority in the industry pyramid, lies the large base of research participants. There is an urgent need to focus on this category of actors and to include them as the central theme of all discussions on clinical trials in India.

Presentation II — The Clinical Trial Scenario in India: Issues and Concerns

Ms Sandhya Srinivasan

This presentation is an overview of some of the major concerns that the booming clinical trial industry poses, and their implications for India. Some of the main points include: government policy, growing scale and size of the drug trial industry, the environment in which it is booming vis-à-vis its implications, sub-contracting of research, concerns over globalisation of trials, and lack of comprehensive information.

Enabling Government Policy

The Indian clinical trials industry is undoubtedly driven by the needs of the multinational pharmaceutical industry. What puts India at an advantage, however, is not only the low costs, ready access to treatment-naïve population, a plethora of acute and chronic diseases that are

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<td><strong>Drug Trial Industry in India at a Glance</strong></td>
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- 670 trials open for recruitment as of 31 December 2010
- Drug company sponsored: 456/670
- Research agenda driven by drug industry
- Foreign sponsors: 292/670
- Large number of foreign companies
- Single largest drug group -- cancer drugs (125/670)
- Research focus on expensive drugs
- Large number of placebo controlled trials – depriving participants of effective drugs?
- Vast majority - Phase III / Phase IV trials for regulatory approval
- Large proportion of ‘me-too’ drug trials
- People ‘desperate’ for healthcare with an inaccessible public health system and unaffordable private healthcare
- Willing collaborators in health systems and doctors

*Clinical Trials Watch, CSER, IJME, 2011*
of interest to industry, and high recruitment rates in clinical trials, but in fact, the changes in law that have provided for an enabling environment. The changes in Schedule Y of the Drugs and Cosmetics Act have provided for a range of incentives, including tax exemptions, fast track approval, and timelines for ethics review. There have also been plans to permit Phase I trials of foreign drugs.

**Strong industry, Weak regulation**

The above-mentioned factors have thus resulted in the creation of an industry that is extremely strong, but is governed by weak systems of regulation. This has resulted in a rise in the number of unethical and illegal trials, as is evident from the increasing number of cases covered by the media over the last year. Some glaring unethical trials covered by the media include:

- **Bangalore:** Infant with cardiac condition died in a pneumococcal vaccine trial meant for healthy infants.
- **Hyderabad:** Adult died in a bioequivalence trial, after repeatedly participating in such trials for money.
- **Andhra Pradesh and Gujarat:** Up to 25,000 girls from vulnerable groups enrolled in vaccine trials without consent, AEs reported during follow-up.
- **Indore:** Government hospital doctors conducted 76 clinical trials on more than 3000 patients, in return for Rs 5 crore.
- **Bhopal:** Gas disaster survivors enrolled in trials without consent.
- **Hyderabad:** CRO administered cancer drug to women without their consent.

### Figure 2

A survey of why people enter a clinical trial showed a clear picture of how CROs/PIs exploit inequity in doctor-patient relationship:

- 75%: investigator is primary physician
- 21%: referred by primary care physician
- 96%: patients enter trials because of their physician
- 31%: patients looking for healthcare, or money
  - for higher quality care: 16%
  - for free drugs/care: 10%
  - for the money: 5%

*Excel Life Sciences, 2008*

**Subcontracting of Research**

Increasingly clinical trials are being subcontracted to CROs. Although there are no official estimates available, according to media reports there are approximately 130-200 CROs operating in the country. These organisations offer ‘turnkey’ services such as recruitment, site monitoring, data collection, as well as negotiating with drug companies. These organisations generally report to their sponsors, in most cases, the drug company itself. It is important to point out that all of them seem to be operating in a legal vacuum.
Over the years, it has come to light that several of these organisations are in collusion with hospital administrations, doctors, NGOs, etc., which often gets them access to patient/participant databases, compiled through a range of sources including hospital databases, health camps, ‘patient education’ programmes, as well as ‘community outreach’ through NGOs.

CROs also offer recruitment incentives to the doctors, including a ‘per patient recruited’ financial incentive, sponsored trips to conferences, institution-based incentives such as 15 per cent of budgeted expenses, department equipment, and investigators’ salaries. This raises pertinent concerns regarding conflict of interests between the investigators and the participants, and a higher probability of overlooking the interests of the participants through the course of the trials. Furthermore, unfair inducement and incentivisation is also used in patient recruitment, thus violating the basic tenets of free and informed consent in the process of recruitment. The participant is often doubly vulnerable due to their relationship with the doctor, which is one of hierarchy and power, as well as a desperate need for better access to healthcare (See Figures 2 and 3).

**Monitoring by Ethics Committees**

It is important to step back and take a look at the role of ECs in order to assess their effectiveness. These committees constituted by the research institutions, etc., in charge of reviewing proposals and monitoring research, are often improperly constituted, poorly trained, and ill-equipped. There is a tremendous pressure from sponsors and institution to approve trials without any delays. There have been several instances, where committees have not been informed about refusals by other ECs at other sites. Several concerns have also been raised with regard to the ‘independent’ ECs, of which there are no official estimates. These committees review industry sponsored proposals for a fee and are not linked to any institution. They have hence created a ‘market’ for ECs, where it is possible for researchers to go ‘EC shopping’ if all their demands are not met by a particular committee.
This again raises important concerns regarding the validity of the proposals approved since the ECs may be inclined to approve proposals for the sole purpose of gaining a fee. This, in turn, results in a total delinking of research from the institution, thus making it even more difficult to monitor such research and its practice.

**Trial-related Injury: Compensation Denied, Requirements not Fulfilled**

There has been an increase in the number of deaths reported over the years, from 132 in 2007 to 670 in 2010. Although 25 out of the 670 deaths have been proven to be related to participation in trials, only five of these cases have received compensation. Moreover, in cases of injuries, expenses have been reimbursed for only eight participants. A study (Thatte, U. et al, 2007) conducted on the awareness of procedures related to compensation and medical treatment, showed that 47 per cent of investigators, and 26 per cent of EC members were either unaware of, or did not understand these requirements. The only compensation policies that the investigators were aware of, were either related to the provision of immediate medical relief, or reimbursement of expenses in this regard, but not compensation for disability or death. Similarly, the informed consent forms also had no mention of compensation; there was a mention of reimbursement, except in cases where the treatment was not already covered by insurance or after the insurance was exhausted.

**Regulation of Clinical Trials in India**

The DCGI’s office that is in charge of all regulatory aspects of clinical trials including the review of applications and monitoring of the trials themselves, has been grossly understaffed and overworked in the face of the exponential growth of the industry. This office, plagued by charges of corruption, has consistently failed to live up to its roles and responsibilities. It has been six years since the regulatory changes encouraging concurrent phase trials in the country were recommended, but India still lacks a central registry of all the organisations conducting trials, of ECs, formal mechanisms of site inspection, AE reporting and compensation guidelines; all these remain in their draft stage. Hence, any information on the industry has been pieced together from press reports, investigations by NGOs, laws and

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guidelines, and a nascent clinical trials registry. Moreover, information such as templates of informed consent form that should have been in the public domain are conspicuous by their absence. In the case of the HPV vaccine demonstration projects, the government withheld details sought under the Right to Information (RTI) Act on ‘public interest’ trials conducted with government support, saying that it was ‘proprietary information’. The industry on the other hand, refused to part with any information, as well as all requests for interviews, saying, “we are answerable only to authorities”.

Thus, some of the major issues and concerns regarding clinical trials in India that need to be addressed on an urgent basis include the following:

- Research agenda: currently based on industry profit not community needs
- Recruitment practices
  - exploitation of unequal physician-provider relationship
  - exploitation of poor people seeking healthcare
- Research designs that put participants at risk of harm
- Research violations resulting in harm
- No guarantee of post-trial access to the community
- An industry without regulation, transparency, and accountability to the public

**Comments by the Discussant and Chairs**

**Dr Samiran Nundy**

- A range of personal experiences over the last 40 years as a clinician conducting clinical trials; as a member of the Institutional Ethics Committee (IEC) of a well known hospital; and as ex Editor of the National Medical Journal of India (NMJII) has led to disillusionment in the systems of regulation and conduct of clinical trials.
- Given the fact that the ECs are overburdened and comprise ill-equipped investigators who have little or no knowledge of ethics, and in some cases, the trial protocol itself is dictated by the sponsors, there is a major concern that the progress of scientific research is proceeding in a very unethical manner.
- Drastic measures and changes in regulatory mechanisms are needed to ensure that trials are conducted in an ethical manner. A suggestion in this regard could be the formulation of an independent regulatory office, akin to the Office of Scientific Integrity present in the US. There is also an urgent need for civil society participation in the regulation of clinical trials in the country.
The clinical trials sector in this country has undergone significant changes since 2005, when Schedule Y of the Drugs and Cosmetics Act was amended. Over the last 7-8 months, the Ministry of Health and Family Welfare (MoHFW) has been looking at the lackadaisical attitude towards the regulation of clinical trials, and closely scrutinising the deficit areas in this regard. The Ministry has been assisted in this exercise by the Parliamentary Standing Committee on Health.

A scenario where the research participants or the human subjects of clinical trials are at the bottom of the pyramid is one of serious concern. The MoHFW hopes to bring to the fore, issues of accountability and transparency amongst the various groups operating in this industry. One such initiative has been to make the registration of CROs mandatory in order to ensure accountability. Once the research is outsourced, the sponsor becomes completely responsible and cannot get away.

Schedule Y of the Drugs and Cosmetics Act is the regulatory mechanism to ensure accountability. Comprehensive amendments were made to Schedule Y in 2005, which provided for concurrent trials in India, and a legal framework for industry accountability. The MoHFW now intends to further strengthen Schedule Y and is looking to civil society for help in this regard, particularly with regard to compensation, and other issues.

The responsibilities of the ECs and investigators have been included in Schedule Y keeping in mind the rights, safety, and dignity of the research subjects. However, these provisions continue to be inadequate. For instance, while specific provisions have been laid out regarding IEC membership, their implementation is questionable. The training of IEC members is also a major area of concern.

The MoHFW will work towards the strengthening of the responsibilities of the different players involved in the trials industry. At present, according to the law, a particular trial site can take clearance from any independent IEC. However, the government is trying to introduce an amendment to ensure that the IECs are institution and area specific.

With regard to compensation, there are three points that require further consideration – establishment of a causal relationship and proof; the quantum of compensation; the procedure of payment. Sponsors often claim that injuries or AEs are not linked with the drug being tested. IEC’s are generally ill-equipped to investigate into these matters. It is in this context, that despite the large number of deaths reported last year in the course of clinical trials, only 22 cases were attributed to the drug and compensation was granted.
• In order to preempt such a situation, the Ministry is thinking of introducing an amendment to shift the onus of proof entirely to the sponsor, who will have to prove within 30 days, that the AE was not caused by the drug being tried.

• With regard to the quantum of compensation, suggestions regarding how a sum may be arrived at, and the indicators that may be used in this context, are being invited by the Ministry.

• There is an urgent need to amend, strengthen and augment the enforcement of Schedule Y and the GCP guidelines. The central government will be allocated Rs 5000 crore to strengthen existing regulatory infrastructure, particularly the roles and responsibilities of the office of the DCGI. The MoHFW will look into the revision of Schedule Y towards making it criminally liable, by including penal provisions.

Ms Brinda Karat

• The industry operates through extremely strong lobbies that work towards pushing the agendas of profit over regulation. With the current government’s one-point agenda to further liberalise Schedule Y of the Drugs and Cosmetics Act, by pushing it towards data exclusivity, restriction on transparency, and weak political wills, it gets difficult to regulate.

• There is an urgent need for the MoHFW, to set up a mechanism to check unethical trials in the communities.

• In the context of what seems to be a deliberate targeting of certain populations for participation in clinical trials in India, there is a need to study the targeting of trials on similarly marginalised populations in the western world. We also need to examine the impact of any changes in the regulations of these countries, on clinical trials in India and other developing countries; for example, the participation and subsequent ban on prison populations in clinical trials in the US, the continued targeting of African-American and other migrant communities in developed countries.

• Further clarification needs to be sought from the MoHFW regarding budgetary allocations made in 2006-07, including tax concessions for the companies conducting trials.

• A serious consideration needs to be made with regard to the violation of clinical trial regulation in India. What is the criminal liability in the case of illegal trials? Should there be a call for criminal prosecution, or does a ban of the said trial constitute ‘appropriate’ accountability measures.

• There is a need to think about the efficacy, ethics, and legalities of the number of clinical trials conducted in the country, as well as the number of participants recruited in the different phases of clinical trials. For instance, for a drug approved elsewhere in the world, is it enough to carry out trials within the country on only 100 participants.
NEW DIVISION OF LABOUR IN COMMERCIALISED RESEARCH

**Discussant:** Dr Amit Sen Gupta, Joint Convener of Jan Swasthya Abhiyan (JSA); AIPSN  
**Chair:** Dr P.M. Bhargava, Founder, Centre for Cellular and Molecular Biology (CCMB); Ex Vice-Chairperson National Knowledge Commission

The first theme to be discussed at the Consultation was related to the division of labour in a scenario where there is an outright commercialisation of research. The presentations in this session as well as the subsequent discussions focussed on the organisation and role of CROs in managing ‘research for profits’. Dr Arun Bhatt from Clininvent Research examined the different business models that may be used to understand the organisation of clinical trials in India today, with special emphasis on the relationships and transactions between the various players involved. He also discussed the dilemmas faced by the CRO industry and the context within which these were located. Ms Deapica Ravindran, from the Centre for Studies in Ethics and Rights (CSER), presented the preliminary findings from a research on Biomedical and Health Experimentation in South Asia, that she has been a part of. She highlighted the perspectives of the various players involved in the clinical trials industry, focusing on the insights from the CROs and the trial sites.

**Presentation I — CRO Industry: Development and Dilemma**

**Dr Arun Bhatt**

This presentation will briefly examine how India has come to be seen as the outsourcing capital of the global clinical trial industry. I will also look at some of the dilemmas that the industry and researchers foresee for themselves, and the context in which these concerns are located.

It is often believed that the West outsources all their trials to India; however that is only part of the picture.

The graphs (Figures 5 and 6), reveal that South Asia accounts...
for only 248 trials out of the 6984 trials being conducted worldwide. North America continues to be a leading site for industry trials with over 3000 trials registered in 2010. I would like to draw attention to Korea, which also conducts a large number of clinical trials. This, however, is not due to its large population, as is often touted, but in fact because of its regulatory policies. In Korea, the clinical trial industry and the Government have jointly made efforts to certify trial sites, a task that India has so far failed to do. Hence, the USFDA has immense faith in the trials held in Korea, evident by the low number of site inspections conducted by the USA; India with 239 trials has had 23 site inspections, while Korea with 341 trials has had only 10. Moreover, recent numbers point towards a steady decline in the number of trials being conducted in India over the last four years.

I. Why Outsource Trials?

Trials are commissioned and outsourced for a number of reasons. According to a study done by Getz and Vogel two years ago, the following reasons were stated for outsourcing:

- **Downsizing**: With a collapse in the markets, companies are downsizing and have fewer employed staff and hence higher management issues.

- **Volume of trials**: Present day regulatory systems demand more trials with a larger number of participants. A trial that could earlier be conducted with 1500 participants now requires a recruitment of at least 4500, in order to be considered valid.

- **Global trial placements**: As the number of patients required for drug development has increased, the companies are selecting countries outside US/Europe for clinical trials to complete clinical trials in time.

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Focus on core competencies: The pharmaceutical companies’ strategy is to focus on their internal competencies in critical areas of drug discovery and development. Outsourcing allows the company’s internal teams to focus on these critical areas.

Control costs: The cost of drug development has increased a lot in the last few years. By outsourcing clinical trials to CROs and placing trials in developing countries, the companies aim to reduce the cost of clinical development.

Safety requirements: The regulatory authorities demand that companies conduct large post-marketing safety surveillance studies in several thousand patients. This requires inclusion of large number of investigator sites globally.

Profitability pressures: The pharma industry is facing generic competition, and high failure rates in new drug development, which affects the bottom line. Hence, companies are looking for cost saving measures like ‘off-shoring’ to developing countries and outsourcing to CROs.

The Indian clinical trials industry is not a small industry and various surveys to assess its size have thrown up different numbers. However, a safe estimate would be approximately $300 million, of which 30–40 per cent comprise CROs. These numbers, however, do not support claims that India and China will surpass other global regions with regard to growth in clinical trial activity and outsourcing.

II. Outsourcing Dilemmas

Some of the main dilemmas faced by an Indian CRO today are:

II.a. Diversity of Models with Multiple Sponsors–CRO teams: The sponsors have shifted from handing over the entire implementation of the trial to the CRO, to using multiple models. The most common model used today is that of a Functional Service Provider, where a trial is divided into multiple segments and different CROs work on varied aspects of that trial. For instance, one CRO will be responsible for writing the protocols for the trials, another will do the implementation, and a third will monitor the trial.

II.b. Sponsor–CRO relationship and communication challenges: The Sponsor–CRO relationship could be represented as in Figure 8. A foreign sponsor hires
an international CRO, which, in turn, hires a local CRO. This local CRO could further hire local vendors such as laboratories, courier services, drug suppliers, etc. This model could get more complex with the inclusion of foreign vendors, and other permutations and combinations, thus resulting in challenges as well as gaps in communication.

In another scenario (Figure 9), the sponsor could be European and the trial could be outsourced to an Italian CRO with a mandate to work with local CROs in the countries where the trial is conducted. This Italian CRO will then hire nine CROs in nine different countries, while at the same time retaining the posts of project management, quality assurance, safety surveillance, data management and statistics with itself. The Italian CRO works with central vendors for electrocardiograms (ECGs), labs, and electrodesiccation and curettage (EDCs), while the local CRO hires local vendors for these jobs. Any communication between any of these players goes through the sponsor via the international CRO before it is sent, thus causing major hurdles. However, this problem can be overcome if the foreign sponsor hands over the trial to a local CRO.

In a third model, the trial is in sourced. In this case, a sponsor hires a CRO to work along with them in their own areas. This model has a lot of advantages over the outsourcing model as it is more cost efficient and the control of the trial remains in the hands of the sponsor. Moreover, given the current trend of economic downsizing, sponsors find it easier to downsize CRO teams rather than their own staff.
Figure 10 represents a sponsor-CRO model of site management. It is often assumed that CROs work directly at the trial sites. However, this is not always the case. Sometimes the sponsors deal with the sites, physician investigators directly and at other times they go through Site Management Officers (SMOs), which are akin to on-site contractors. SMOs take care of all issues at the site on behalf of the investigator, ranging from EC approvals to recruitment of participants.

A clinical trial is a long process as displayed in Figure 11, where each step can be outsourced to different agencies.

**III. Selection Criteria**

CROs are generally selected by sponsors on the basis of certain criteria. These include, first and foremost, organisation’s experience and area of expertise; a strong reputation for quality, speed and cost; the ability to deliver patients; the speed of turnaround of a proposal and finally, a significant cost advantage.
IV. Sponsor - CRO Communication

This involves a complex system (Figure 12), with several members communicating with each other across various levels. This results in challenges related to management, accountability, responsibilities, etc. According to a recent survey on the functioning of CROs in India, there is a mismatch between the expectations of the sponsors and the CROs on issues such as quality and quantity, which are not covered in typical Request for Proposal (RFP) or Measurement System Analysis (MSA) templates.

V. Quality and Compliance

FDA site inspections are of prime importance to CROs. Figure 13 reveals that out of the routine inspections conducted, 40 per cent resulted in no action taken, with very minor findings, but no major issues; 59 per cent were in areas with some issues and voluntary action was indicated, but no warning letter was issued and no criminal liability was assigned. In case of a serious suspicion, however, a ‘for cause’ inspection maybe undertaken.
If the suspicion is confirmed, official action may be taken. Over the past few years, cases of ‘official action required’ have remained constant at 23 per cent.

In the US, the common problems highlighted during site inspections involve protocol compliance (39 per cent), record-keeping (29 per cent), consent (13 per cent), drug accountability (7 per cent) and AEs (7 per cent). In India, there have been 23 USFDA site inspections, with no official account of DCGI inspections. The FDA trial inspections have found 12 sites with no findings (52 per cent), and 11 sites with some findings (48 per cent). The findings at these sites revealed inconsistencies such as inadequate and inaccurate records, inadequate drug accountability; failures to follow investigational plan, to notify the Institutional Review Boards (IRBs) about changes and to submit progress reports.

The FDA also carries out inspections with regard to the IRBs and the ECs. Although IRBs are on the radar of the DCGI as well, not much has been done in this respect over the years. The common problems highlighted during the FDA inspections of IRBs include non-adherence to written procedures, improper maintenance of minutes, overlooking of consent protocols, slack review processes; lack of quorum, expert review and continuity.

With regard to sponsors, some of the common findings include:

- Inadequate monitoring and unqualified monitors.
- Failure to secure investigator compliance, to submit progress reports, to notify the FDA, investigators, or IRBs.
- Inadequate product accountability.
- Failure to obtain signed investigator agreement, to obtain FDA or IRB approval.

**VI. Systemic Errors in Clinical Trial Conduct**

There is an urgent need for the creation of a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. This will ensure that the data reported is credible as well as accurate, and that the rights, integrity, and confidentiality of the trial subjects are protected. However, in the current system the protocols and ancillary documents are poorly designed and executed. There is an inadequate internal process to ensure the integrity of critical study activities (e.g. randomisation).

In the absence of standard prescribed procedures, the reliability of the trials cannot be guaranteed; for example, recently, discrepancies were uncovered in the trials for Telithromycin. During the course of this trial, the CRO discovered evidence of fraud at the trial site and duly informed the sponsor.
The sponsor however decided to take no action claiming that they were unaware of the fraud. Finally, the FDA found evidence of extensive fraud and sent a warning letter to the sponsor. In the case of the Ceftobiprole trial, a warning letter was sent both to the CRO and the company. However, sadly, these continue to be examples of mere warnings since there has been no criminal liability so far.

**VII. Division of Responsibilities**

“...CROs that encounter problems with trials and want to act honorably and correct them rarely go directly to regulators, instead reporting any concerns to their drug-company clients — but they apparently don’t always get an appropriate response” (Dr Miriam Shuchman, NEJM, 4 October 2007).\(^9\)

**Figure 14**

<table>
<thead>
<tr>
<th>Process</th>
<th>Sponsor</th>
<th>CRO</th>
<th>Investigator</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Performance</td>
<td>✓ ✓</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Monitoring</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Auditing</td>
<td>✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Recording</td>
<td>✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Analyses</td>
<td>✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Reporting</td>
<td>✓ ✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Accuracy and Credibility of Data</td>
<td>✓ ✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Participant protection</td>
<td>✓ ✓ ✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

This quote above represents the current situation with the CROs, where they find it very difficult to go to the regulators and mostly go back to the sponsors. This is for business reasons, as well as due to the fact that there is a complete absence of approachable regulatory mechanisms. As per the GCP guidelines and definitions (Figure 14), the responsibility for all aspects of the trial lies first and foremost with the sponsors. The CROs are responsible

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only for those aspects of the trial that have been outsourced to them, such as the conduct, performance, and in some cases, monitoring and recording of trials, etc., while most of the on site responsibilities lie with the investigator. The ECs are responsible mainly for the protection of participant rights as well as for overall monitoring of the trial.

However, the GCP guidelines do not take into consideration the other players in the industry such as the SMOs. The Division of Scientific Investigators (DSI) has made a pertinent observation in this matter:

“FDA regulations do not reflect the current landscape of clinical trials in that there are many third parties involved in clinical trials who have the capacity to impact data integrity and/or human subject protection and these parties are not currently under FDA jurisdiction”.10

Some of the main issues in this regard are related to inefficiencies in key documentation and governance. In addition to this, the responsibilities of the various players are also not clearly defined. Often, there are misunderstandings between the sponsors and CROs with regard to the terms and conditions. Moreover, while there may be several changes in duties over the course of a trial, these are not documented in writing. With regard to governance, there is a limited real-time assessment of whether a CRO is fulfilling its responsibilities, and how it is going about it. There is also an absence of comprehensive analysis of the root causes and corrective action when issues are identified during the trial.

Given these concerns, some recommendations by regulatory bodies include:

- Communicate specific policies, procedures, study requirements, and responsibilities to involved company staff, CRO and service provider personnel, clinical investigators and their staff.
- Build quality into clinical development programmes.
- Apply risk management principles to effectively assign resources to activities that present a greater risk to trial and application data integrity, human subjects’ protection.
- Define controls to prevent errors and identify potential problems and intervene before issues become endemic.

As of 23 September 2011, the total number of clinical trials registered in the Clinical Trial Registry of India (CTRI) was 2015. Also, 3272 identifiable institutes and organisations have been listed including hospitals and nursing homes, where simultaneous trials may be ongoing across various departments. The data also registers 423 non-identifiable institutions. Some of the data collected from Tamil Nadu and Maharashtra between 2010 and 2011 is depicted in the tables in Figures 15 and 16.

From the data of the two states, it is evident that there is a preference for private hospitals as sites for research. Also, the number of trials per PI is highest in the metropolitan cities. However, qualitative research suggests that trial sites are shifting from metropolises to smaller cities and towns. Some of the reasons for this shift that have emerged from the study, include saturation of PIs in the metropolises, stringent ECs in established hospitals, and improved infrastructure in the smaller towns and cities.

Preliminary findings about host motivations and experiences based on analysis of 27 interviews with site staff, including 11 PIs, 5 Co-Investigators (Co-Is), 10 Clinical Research Coordinators (CRCs), 1 manager and 2 people who were in charge of research in their institutes, are presented here.
Findings

Role Division on Site

PIs are the most important players for the implementation of protocol at the site. PIs delegate work to Co-Is, who may be doctors or assistant professors in the same department. These Co-Is (and sometimes PIs) conduct and confirm all clinical investigations.

Next in line are the CRCs, who run the daily operations, which include documentation, patient recruitment, data input, patient follow up, communication with the CROs, responding to outside queries, EC documentation, etc. With regard to the consent-taking processes, all players admitted to being involved in the process.

Motivations

Becoming a CRC is a lucrative career option for many fresh graduate students from a wide range of disciplines such as Ayurveda, Homeopathy, Life Sciences, Pharmacy, Dentistry, etc. Most of these graduates generally also have a post-graduate degree in clinical research. However, retaining the CRCs is often difficult as they are offered high salaries and posts after just two years of experience. Thus attrition rate is very high within the CRO industry.

PIs and Co-Is provided one or more of the following motivations for joining the clinical trials industry.

- Patient benefit – access to new medication otherwise unavailable or unaffordable for patients.
- Monetary gains (personal, as well as to do their own research).
- Access to better infrastructure and improved facilities.
- Advancement of science.
- Boost for curriculum vitae (CV) and research skills.
Despite the benefits, not all PIs are enamoured by the industry as they do not have any emotional attachment with the study at hand, and merely consider it to be part of their job profile.

One of the investigators stated:

“Sponsored trials do not offer that much incentive, apart from the financial, of course, because the main reason one does studies, that research question has to be yours; that feeling is not there for multi-centric sponsored studies. The research question is not yours so we don't have that so called emotional attachment with that study”.

Most of them denied being intellectually stimulated by clinical trials:

“... A lot of it is mechanical and the research coordinators do most of it. You just sign on the dotted line once in a while when it is needed. It doesn't stimulate you as much as it would if you would design the trial yourself”.

Some CROs look at clinical trials as a way of building local knowledge and capacities:

“This will help them to get organised, they can also learn to understand the protocols, the diseases and the people. One understands these better, we also learn documentation, otherwise we are not disciplined, and a trial helps us to be disciplined”.

“It builds capacity in terms of making people understand the process - consent, randomisation, recruiting subjects, strategies around that - and that is some capacity building. The problem with industry driven studies is that the protocol is written by someone else, you're just an implementing agency. So you don't understand the nitty-gritty of writing a protocol, doing research, asking the questions yourself”.

However, it is also recognised that these capacity building efforts are skewed to further contribute to the industry itself:

“.. The academics have started to shape themselves based on clinical trials, which is really pre-cooked research, it is not research, it is operations. And I think it is a dreadful thing that has happened to India. India is becoming a service centre-economy for the middle class, extending to academics and research”.

Comments by the Discussant and the Chair

Dr Amit Sen Gupta

- While the two presentations have posited on an aspect of this new division of labour, there is a need to step back and look at the larger picture. We need to understand how
this knowledge is created, owned, and disseminated. For instance, we are now faced with a situation where knowledge is created and disseminated by the West, with the outsourced clinical trials forming only a small part of this exercise, yet following terms set by the creators.

- The shift in the location of trials outside of the US can also be linked to the ban on research on prison populations in the early nineties. It is extremely important to study these allegorical links. Moreover, with a change in Schedule Y in 2005, an opportunity was created for the West to use the developing world to enhance their knowledge base by exploiting the human resources to generate knowledge.

- The crux of the debate is how these trials can be conducted ethically in India. While the example of Korea may be interesting to study, one also needs to look into the larger socio-political context of our country. Do these clinical trials contribute to better health in the country in any way? While on the one hand, clinical trials are being vigorously promoted, on the other, practically no scientific research capacity is being built. The increasing labour force involved in the industry, appears to be merely a form of indentured labour of the 21st century.

**Dr P.M. Bhargava**

- There are very few trials being done on diseases that are relevant to India’s public healthcare needs; for example, there is no drug development for diseases such as Kala Azar. Similarly, there seems to be no standard model for the testing of traditional medicines.

- The term Contract ‘Research’ Organisation is a misnomer as these organisations are not conducting ‘research’ in the true scientific sense of the word; they should, in fact, be termed as Clinical Trial Organisations.

- It is important to closely study the phenomenon of the outsourcing of clinical trials to countries such as India with a view to ascertain what can be outsourced, where the trials can be conducted, and the numbers required for the trial. This will help us to create a set of criteria that can be a benchmark for the industry.

- The problems of clinical trials are closely related to the problems of medical ethics in India. Corruption plays a big role in these problems as the emphasis is on money-making rather than on service provision or liberalisation. Corruption has hence adversely affected the framework in which we have to look at clinical trials.

- There appears to be a complete lack of ethics in all scientific endeavours in India. There is a need for an independent body akin to the Office of Scientific Values that is a part of the National Institutes of Health (NIH) in the US.
Discussion Points

- There is an urgent need to further explore the legal void that CROs function in currently. One also needs to look into corruption at the bureaucratic level and the fact that the office of the DCGI and the CROs must also take on the responsibility of getting approvals within the desired time frame for their sponsor companies.

- It comes as no surprise that several lifestyle drugs are tested by foreign companies as there is a huge market for them in the host country. However, the real question should in fact be, to what extent are attempts made to strengthen local capacities of Indian researchers and pharmaceutical companies, and to accordingly get disaggregated data on the number of trials conducted by local pharmaceutical companies, vis-à-vis foreign companies.

- There is a need to understand the phenomenon of downsizing of the clinical trials industry in developed countries, and how it is related to an underlying profit motive. A cross-sectional picture of growth and trends in Asian countries including India, would help to promote this understanding.

- The vast variance in literature with regard to the scale of the clinical trial industry needs to be understood in the context of the CTRI, which despite being mandatory for the last two years is unable to provide a comprehensive registry of the clinical trials being conducted in India.

- It is important to acknowledge the history of CROs in the country in the context of local pharmaceutical companies wanting to find a place in the post World Trade Organisation (WTO) regime.

- It is important to consider the legal recourses one can seek in the case of non-compliance. It has to be legally established, who bears the liability; whether the indemnity clause applies to CROs or to the sponsors.
This session focussed on the main theme of the Consultation - the regulatory standards in India today. The four speakers examined and critiqued each of the existing mechanisms of regulation, and came up with suggestions for strengthening these structures. Dr Amar Jesani of IJME, through his presentation, explored the historicity of the Ethical Guidelines for Biomedical Research on Human Subjects outlined by the Indian Council of Medical Research (ICMR). He also examined how these guidelines could be enforced. Dr V.M. Katoch, Director General of ICMR, highlighted the role and importance of the ICMR guidelines. Dr Vasantha Muthuswamy’s, ex-Deputy Director General of ICMR, presentation analysed various aspects of the Draft Bill by the ICMR on Human Subject Protection. The last presentation by Dr C.M. Gulhati from the Monthly Index of Medical Specialities (MIMS) briefly talked about Schedule Y of the Drugs and Cosmetics Act (DCA) and moved on to critique the amendments made to it in 2005. His presentation also highlighted some of the areas of ambiguity in Schedule Y, and proposed strengthening measures.

**Presentation I - The ICMR’s Ethical Guidelines for Biomedical Research on Human Subjects**

*Dr Amar Jesani*

Talking about ethical guidelines and ethical standards for biomedical research in India, and assessing what the ICMR has done on the subject is a formidable task. However, at the same time, it is extremely important to take a critical look at what we already have and what we have been able to achieve. Through this presentation I will explore the need for governance of biomedical research, the various elements of governance, the ethical guidelines, and the role of the ICMR. I will also draw attention to some issues regarding the principles and standards set by the ICMR guidelines as well as the ECs.

**Regulation of Research**

It is very important to keep in mind that research is a specialised activity and is very different from the kind of work that is routinely done in medical and public health practice.
Researchers approach participants to ask them to be a part of a process. Through this process, the researcher discovers something and announces it as new knowledge.

Therefore, a researcher has a greater obligation towards a participant than a doctor towards his patient. However, this is not always obvious because we talk about ethical guidelines in research, but very little is said about ethics in medical practice. There has been a lot of denial around this, and the doctors are against any aspersions being cast on their ethical standards. It is for this very reason that we need to create a governance structure to regulate systematic research activities, and to define scientific as well as ethical standards, both of which go hand in hand. Such a demand is generally triggered either following a human rights violation, or due to an increasing consciousness about the human rights of research participants, which provides the basis for ethical standards. Science ought to be pursued for the betterment of society and in conformity with human rights and ethical standards.

Assessing Research Governance - Some Elements

It is important to outline a few concepts before I talk about the ICMR guidelines. My first point pertains to the relationship between ethical and legal standards. Do the ethical guidelines developed for research, measure up to the legal standards, and are they legally enforceable?

My second point is regarding the establishment of governance structures, which in India, are represented by the office of the DCGI and by the EC. There are also reservations regarding regulatory bodies. These reservations cannot be addressed unless there is transparency, and it is proven that the regulatory bodies can function independently of the people they are supposed to regulate. But how does one set standards for such a regulatory body? It can only be done when there is accountability of these structures as well as of the people operating them.

Ethical Guidelines

In general, ethical guidelines deal with ethical principles, and provide guidance for implementing these principles in a specific research context. On certain issues, they may be directives that codify specific rules to be followed; on others issues, they may leave room for flexibility or discretion in their interpretation, by the regulatory body. Thus, it is important to study both the directive and the discretionary elements of the guidelines in order to discern the purpose or the motive behind its formulation.
There is no doubt that these guidelines are a product of history, and have been shaped by power equations and material needs of a given time, and are continuously being re-shaped by changing power equations even today.

**Ethical Guidelines by the ICMR**

The ICMR has, from time to time, brought out certain ethical guidelines in order to try and regulate the clinical trials industry. In 1980 – the Policy Statement on Ethical Considerations involved in Research on Human Subjects, in 2000 and 2006 – the Ethical Guidelines for Biomedical Research on Human Subjects or Participants.

It is pertinent to note that these guidelines pre-date the phenomenon of large-scale commercial product development oriented biomedical research in India. Why then did the ICMR feel the need to develop guidelines way back in 1980? Was it to promote further research by the World Health Organisation (WHO) in India, including in newer forms of contraceptives.

Similarly, the 2000 guidelines came five years before the amendment of Schedule Y. What were the events that prompted the formulation of these guidelines, and what was happening at that time in the scientific community? Was it because of the scandal that broke out in 1997 over the observational study for cancer of the cervix in a large number of poor women, which was conducted without their consent or treatment? Or did India plan to get involved with the WTO?

The Drugs and Cosmetics Act (Schedule Y) does not convert ethical standards into legal standards; the enforcement of ethical standards is left to the Research Ethics Committees (REC).

The ICMR guidelines, 2006 is an extremely well written, comprehensive, and highly informative document that draws from national as well as international experiences. It has an extremely wide scope that deals with the guidance and standards of ethical principles, starting with general principles: ethical review procedures (or procedural ethics for the regulatory functions of RECs), general ethical issues and standards, specific principles and guidance for biomedical product development research, epidemiological research, human genetic and genomic research; research in transplantation, and research in Assisted Reproductive Technologies (ARTs).
Discussion on Principles in the Guidelines

Principle of Essentiality: The principle of essentiality states that research should not be carried out unless it has a scientific validity, a social relevance, and social utility in the local context. However, this throws up certain questions:

- Scientific validity is an integral part of ethics review as unscientific research is unethical.
- How does one assess social relevance and utility?
- Do we need to make research a national priority in order to implement this principle? If so, what are the national consultations and dialogues that need to take place to make it a national priority?
- How does one separate ‘necessary’ research from the ‘me-too’ research?

Principle of Maximisation of Public Interest and Distributive Justice: This principle addresses the issue of the application of research outcomes for the benefit of the least advantaged, i.e., the participants and their communities. Unfortunately, the guidelines have somehow overlooked one of the most important issues, post-trial access to drugs. In a best case scenario, the participants may have access to the new drug for a limited period of time, but this is considered as an inviolable ethical standard. Moreover, the ECs and investigators have no power over the post-trial market price and hence affordable access to new drug by these communities. Who should be held responsible for this; the DCGI or the ICMR? It is important to have a mechanism for deciding and implementing such issues, or else it remains merely an expression of interest with no action.

Principle of Non-exploitation: Non-exploitation is an absolutely essential feature of research, and should cover issues such as benefits (including post-trial benefits), remuneration and compensation, ancillary care, provision of complete information, respect for autonomy, transparency, etc.

- How does one avoid exploitation in a situation where standard care is either not available, or not affordable? (in the of absence of universal healthcare coverage)
- Should all research participants be covered by a comprehensive health insurance in order to promote non-exploitative relationships in research?
- How should adverse events (AE) be assessed and who should be given the task of assessing them? Can exploitation of the participants be prevented if AEs are assessed only by the sponsors or their paid agents? It is important to have a mechanism that can independently assess AEs.
Who determines the compensation for research injuries or deaths, and what are the criteria used to arrive at this compensation?

Who is responsible for ensuring that the victims are compensated?

How does one weigh the benefits provided to avoid exploitation against ‘incentives’ ‘undue inducement’?

**Principle of Autonomy, Voluntariness:** As per the guidelines, it is obligatory for investigators to obtain consent from their patients, thus turning physicians at the research site into investigators. There is an urgent need for the patient information sheets and informed consent forms (as provided in the approved protocol of research) to be made public without any Intellectual Property (IP) or trade secret attached to them. Can the consent of a community or a cluster acquired through village leaders, panchayat heads or tribal leaders be acceptable?

**Governance and Regulatory Structures - Research Ethics Committees**

Guidelines seem to favour, a priori, the institution-based research ethics committees (RECs) for ethics review and overseeing of research. The 2006 guidelines also accept, in addition to IECs, for profit or not for profit, private ECs. There is no evidence to show that the IECs (institutional or private) are the best structures to implement ethics standards for the protection of participants in India. No attempt has been made to propose, even for experimental purposes, publicly funded local, regional and national ECs. The most crucial requirement for a robust regulatory system is the systems independence from institutions, sponsors and researchers. The only standard for independence of ECs is currently limited to having external chairperson, a standard that can be easily manipulated. Standards for independence should include independent appointing agency, independence of funding support, etc. In addition to this, the regulatory structures should also include:

- A high proportion of representation of patients, their advocates and lay people.
- Strict standards for transparency and accountability of EC members.
- A code of ethics for the EC members.
- The law drafted by the ICMR for ECs to be made public.

I would like to conclude by commenting on the dismal state of the moral regulatory structures. There is an urgent need to convert ethical standards into enforceable legal standards and re-examine site or institution-based private regulatory structures. We need to make a transition to publicly funded local, regional, and national ethics regulatory bodies. We also require a legal framework for overseeing these ethics regulatory bodies, with mandatory transparency standards and accountability for its work.
Intervention on Ethical Guidelines

Dr V.M. Katoch

The last decade has witnessed several changes vis-à-vis ethical standards, with more and more questions being asked and answered, reports being sought and produced, and symposia being organised to discuss the ICMR guidelines. There is a very urgent need for the strengthening of regulatory mechanisms in the area of clinical trials today, and it is important to look back and see where we stand today and whether enough has been done in this regard.

The guidelines are being revised and will soon take the form of a Draft Bill, but they are currently unfortunately lying with the Administrative Department of Health Research, of the MoHFW. The old Bill had become extremely outdated and inadequate for the present scenario, which calls for much more stringent guidelines on issues such as criminality, formation of committees, etc. The Bill has now been redrafted and is being put into legal language, following which it will be placed in the public domain for suggestions through a consultative process. Hopefully, by next year, the Bill will be presented in the parliament.

However, even though a structure may be put in place, it is important to define the roles and responsibilities of every player. There is a need for clarity of roles and responsibilities, which need to be defined and made uniformly enforceable. This will be a people’s law and will not be drafted in isolation.

The recent experiences of the HPV vaccine projects in Andhra Pradesh and Gujarat have brought to light a number of issues and problems related to the execution of clinical trials today. Firstly, despite common ICMR guidelines, there are differences in the performance of projects across different States. This throws up the question whether the same institute that has made the guidelines, can also play the role of a regulatory body or act as a partner. At the same time, if it does indeed become a partner, how can it then monitor the performance? In addition to this there are questions of dubious consent, due to varying interpretations of ambiguous clauses in the guidelines.

The second issue involves the exploitation of the marginalised communities. It is a well known fact that drugs are produced purely for monetary reasons. However, such trials must not be conducted in communities that have no stake in drug development. The poor should not be involved from the start.

The third issue relates to post-marketing surveillance and Phase IV trials. There is a severe lacuna in this regard as the trials remain under the ambit of the drug companies, with no independent surveillance bodies. Competent government agencies need to take control of these trials and carry them out in a systematic and unbiased manner.
These issues are extremely critical, particularly now, when we are in a transition mode and moving towards a legally enforceable, clearly defined law. The blurring of the lines between the regulator and the business is of utmost importance and the separation between the two should be clearly demarcated. Hopefully, the Draft Bill will resolve all these issues.

Presentation II - Proposed Bill on Human Subject Protection in Health Research

Dr Vasantha Muthuswamy

Ethics, Guidelines and the Law

The Guidelines or the Laws on ethics, fundamentally cover the morality or the moral code of conduct in the field of biomedicine in India today. The guidelines, that have so far benefited the society, will now be replaced by a law, which will be legally enforceable and controlled by the State.

The ICMR first came up with the draft guidelines in 1980. This was an extremely useful document, but it had to be modified first in 2000, and then again in 2006, when it was finalised. This was because of a time lag between the first drafting and the finalisation of the guidelines, to account for the changes in the industry, science and technology in these years. An important point to note is that when the committee was formed in 1996 to look at the 1980 guidelines, Justice Venkatachalliah accepted the Chairmanship of this Committee only under the condition that the guidelines would someday be converted into a law that would be implementable and legally enforceable. Unfortunately fifteen years after, this is still a distant dream.

There are two branches of bioethics; the ethics of medical practice and the ethics of biomedical research. Biomedical research includes all kinds of research that is governed by the ICMR's ethical guidelines. While there is a comprehensive law (Prevention of Cruelty to Animals) that governs various aspects of research with regard to animals, unfortunately, we still do not have a Law that governs research on human participants. There are various parallel acts, such as the Drugs and Cosmetics Act, Pre Conception and Pre Natal Diagnostic Techniques Act (PC & PNDT Act), etc., but there is no singular comprehensive act. Amendments over the years have been superficial, with no consultation or public awareness.

The 1996 guidelines were finally released in the year 2000. However, not all areas of research were covered under these guidelines. Certain concerns such as EC review procedures, informed consent, re-consent, vulnerable populations and waiver, post-trial access, disaster
and emergency research, clinical trials for herbal or traditional drugs, and newer technologies such as ARTs, stored tissue research, DNA banking, stem cell research and therapy remained grey areas (See Figure 18). It was to counter these issues that new guidelines were formulated including those for ARTs, stem cell, etc. Thus, with developments in scientific research, and the resulting moral issues of wrong and right, there is an urgent need for the guidelines and laws to be revised to suit the times, and to rise to the challenges that are posed as a result of these changes. Moreover, these standards differ from country to country and we in India, need to have guidelines that work for our country.

While talking about the rights and welfare of human subjects, the two most important things that come to mind are independent review and a robust and informed consent process. By independent review, we do not simply mean the independent EC, in the sense of the term used today, but in fact a committee that is independent to take decisions without the influence of any other motivating factors. Unless there is a way to make these processes mandatory through regulation, the guidelines will not serve their purpose. While these two issues are fairly well established in the guidelines, there is a major lag in their implementation, due to the non-mandatory and non-legal nature of the guidelines.

Several other issues also continue to plague the arena of clinical trials in India, including the use of placebos, standards of care, community consultation, post-trial benefits, international collaborations, and the dilemma of inducement versus compensation. While Schedule Y addresses some of these concerns, it is limited to clinical trials and leaves out a range of other ethical issues.

**Need for Laws Related to Research and Ethical Guidelines**

Inadequate regulation, enforcement and monitoring, ignorance of participants and researchers, poverty, poor ethical review procedures, and exploitation by sponsors are some of the problems faced by the clinical trials industry. Hence, top priority must be given to the enactment of the guidelines, so that they can have a legal mandate and be universally enforceable. In addition to this, mechanisms of enforcement and provisions related to remedies and advancement of technologies on the basis of cultural integrity also need to be worked out. These include paternity in artificial insemination, commoditisation of the

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**Figure 18**

Technologies with Ethico-legal Implications

- Prenatal diagnosis
- Gene therapy
- Genetic engineering
- Transplantation
- In-vitro fertilisation
- Preimplantation diagnosis
- Embryo manipulation
- Stem cell research
- Pharmacogenomics
- Vaccine development
- Cloning
- DNA banking
female body, trafficking of babies born though surrogate mothers, status of human being in the embryo stage, selective abortion, trading of human organs in transplantation, Intellectual Property Rights and Patent issues, tissue and data banking, etc.

**Biomedical Research on Human Subjects (Regulation, Control and Safeguards) Bill, 2007**

The Bill addresses head on, the issue of ‘accountability’, which is an important tenet in ethics. Accountability is entailed by responsibility, and anyone who is responsible is thereby accountable. To be responsible is to be answerable for judgments, acts and omissions (refusals or failures to act) where appropriate, and in whole or in part. Accountability is also a state of responsiveness, readiness, or preparedness, to give an explanation or justification for one’s judgments, intentions, acts and omissions to the relevant others (stakeholders), when appropriately called upon to do so. For instance, the EC is responsible for going through all research proposals, and monitoring the trials, thereby being accountable for the research as well. This new bill will hence regulate the ECs.

**Scope of the Bill**

The Bill will:

- Promote and regulate biomedical and behavioural research on human subjects to ensure safety and well being of the research subjects.
- Control and monitor the application of new technologies, for example, stem cell research, therapeutic cloning, ART, genomics, etc.
- Prevent unscrupulous clinical trials on unsuspecting patients.
- Facilitate harmonisation with International Guidelines.
- Legalise the ethical guidelines formulated under the Chairmanship of Justice M.N. Venkatachalliah.

**Schedule Y of the Drugs and Cosmetics Act: A Critical Review**

*Dr C.M. Gulhati*

This presentation is aimed at throwing open more avenues for discussion in the area of clinical research in India today. The Drugs and Cosmetics Act is accompanied by a set of rules that may not be passed by the parliament, and can therefore be changed subsequently. Schedule Y is included in the rules, and deals with various aspects of drug trials in India, right from approval to the submission of the collected data. The Central Drugs Standards and Control Organisation (CDSCO), headed by the DCGI, administers it. It was notified for the first time on 21 September 1988 and the first major change was made to it on 2 June 1989.
Schedule Y: the Objective

Definition of ‘New Drug’

A new drug, as defined in Schedule Y is:

- A new substance used for prevention, diagnosis, or treatment of disease in man or animal. A drug already approved for certain claims, which is now proposed to be marketed with modified or new claims, namely indications, dosage, form (including sustained release dosage form), and route of administration.

- A fixed dose combination (FDC) of two or more drugs combined for the first time in a fixed ratio, or a change in the ratio of ingredients in an already marketed combination, with certain claims such as indications, dosage, form (including sustained release dosage form) and route of administration.

- All vaccines shall be considered new drugs.

- A new drug shall continue to be considered as new for a period of four years from the date of its first approval, or its inclusion in the Indian Pharmacopoeia, whichever comes earlier.

Regulate the Entry of a 'New Drug'

In principle, Schedule Y was formulated to regulate the import and/or manufacture of new drugs. It provides a mandate for Phase III clinical trials before the entry of new drugs discovered and marketed abroad. This ensures efficacy and safety for Indian patients, as well as for all phases of trials (animals, humans - Phases I to III) for new drugs discovered within the country. It also encompasses post-marketing surveillance studies to ascertain side effects, dose adjustment, etc., in Indian patients.

Significant Amendments

Figure 19 reveals that prior to 2005, Phase I trials were not permitted in India for foreign drugs, with the exception of drugs with specific reference for use in India, in which case a trial could be carried out. Now, there is no such restriction and Phase I trials are permitted in India if they have been completed abroad.

<table>
<thead>
<tr>
<th>Figure 19</th>
<th>Schedule Y: Significant Amendments in January 2005</th>
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</thead>
<tbody>
<tr>
<td><strong>Pre-amendment</strong></td>
<td><strong>Post-amendment</strong></td>
</tr>
<tr>
<td>• Phase I: not normally allowed</td>
<td>• Allowed provided completed abroad.</td>
</tr>
<tr>
<td>• Phase II: Minimum subjects 10-12 at each dose level at 3-4 centres.</td>
<td>• Minimum number of subjects to be enrolled and centres removed.</td>
</tr>
<tr>
<td>• Phase III: Minimum 100 patients at 3-4 centres, with placebo or standard drug as control.</td>
<td>• All conditions removed including controls (placebo standard therapy).</td>
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With regard to Phase II, the minimum number of subjects was pre-defined at 10-12 at each dose level in 3-4 centres. This number is now left to the discretion of the DCGI. Similarly, with Phase III trials also all conditions were removed, including controls over placebo therapy.

Some of the other major changes include removal of a mandatory phase lag, and authorisation for concurrent trials. Thus, earlier, if a company wanted to conduct Phase III trials in India, it had to complete this phase of trial abroad before any testing on Indian participants. However, today, trials can be conducted simultaneously, as long as the earlier phase has been completed in at least two countries.

Before 2005, there were no Independent ECs; also post-marketing surveillance was mandatory with prior approval regarding protocol and investigators from the DCGI. However, after the amendment, while post-marketing surveillance remains mandatory, prior approval by the DCGI has been done away with.

These amendments clearly display the interplay of liberalisation and globalisation, and the changes in the Indian regulatory mechanisms in relation to clinical trials.

**Additions to the Rules**

By and large, the salient points remain the same as before 2005, when the amendments were made. However, some clauses have been expanded upon and explained in further detail. A provision has also been made for additional pharmacokinetic studies. The importance of Good Clinical Practice has been added, and the reporting of serious adverse drug reactions have been made time bound. All adverse reactions have to be reported within twenty-four hours to sponsors, within seven days to the EC, and within fourteen days to the DCGI. Another provision was made to make the patient information sheet in non-technical language, to make it more understandable for the patients. Although this was mandatory, in practice, this is often not carried out.

Further, the rules also made provisions for trial related injuries to be covered by GCP and ICMR guidelines. However, whether this is adequate or not, remains debatable. As regards the sponsors, they now include medical colleges, hospitals and ‘other facility’. The term ‘other facility’ is, however, not defined and we find that a third of the trials are

<table>
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<tr>
<th>Year</th>
<th>Approvals</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>2007</td>
<td></td>
<td>137</td>
</tr>
<tr>
<td>2008</td>
<td>563</td>
<td>288</td>
</tr>
<tr>
<td>2009</td>
<td>488</td>
<td>637</td>
</tr>
<tr>
<td>2010 (Oct 15)</td>
<td>523</td>
<td>668</td>
</tr>
</tbody>
</table>

CDSCO
taking place in private clinics. According to another provision, the EC must comprise a minimum of seven members, while maintaining a quorum of five, with the Chairperson being an outsider. Approval from distant EC has been permitted and Post-Marketing Trials (Phase IV) have been permitted.

Compensation to Victims

Up to December 2010, there is no evidence or record of any payments on account of loss of income, morbidity, temporary or permanent disability. Compensation has been given to the families of twenty-two persons who died in the year 2010 (Figure 21).

The quantum of compensation was not only grossly inadequate but also arbitrary; an act of collusion among the sponsors. The patients were of different ages and came from very different backgrounds. But no consideration was given to these relevant factors while determining the compensation. This was an abuse of monopoly by the sponsors and a violation of the rules of the Competition Commission of India (CCI).

Major Concerns with the Drugs and Cosmetics Act

- Discretionary powers: These are increased without any supervision and monitoring.
- Qualifications: The investigators and institutions not codified.
- Injury: No credible or transparent system to determine morbidity and mortality, except total reliance on investigators, ECs and sponsors.
- Compensation: No transparent and fair system; total reliance on investigators, ECs and sponsors.
- Appeal: No redressal system for aggrieved patients and families.
- Ethics Committees: No effective system to ensure their proper composition, functioning, and decision making.
- EC hopping: No system to stop.
- Conflict of interest: No procedure to determine and manage such situations.
Violations by sponsors, investigators: No penalty for any violations.

CROs: Entry without any scrutiny or regulation.

Comments by the Discussants and Chair

Mr S. Srinivasan

- New technologies need clinical trials; they need to establish superiority over existent ones. However, I would like to propose that no clinical trials be done on vulnerable groups unless special circumstances are proven.
- Uncertainties in Schedule Y result in undue discretionary powers of the DCGI.
- Today a lot of drugs are unscientific and irrational; there is need for reflection over the approval of trials for such drugs. It is very difficult to remove an unscientific or unethical drug from the market, hence calling for stringent post-trial supervision of drugs.
- CROs are middle men and do not have a role in promoting research or generating capability. We need to consider either banning, or introducing caveats in their functioning.
- The Draft Rules for registration of CROs is purely for registration and has no safeguards or punitive provisions. There is an urgent need for accountability of ECs, and compulsory publication of all clinical trial data and study findings in the public domain.
- How can unethical procedures be made illegal? We need to consider how to establish legal culpability in case of violation of the basic principles and tenets of ethics.

Dr Mala Ramanathan

- We need to consider the fact that the guidelines operate in a context of weak ethical practice and insufficient information on applicability. There is an urgent need to look at independence and transparency (of research regulators, institutions, and sponsors).
- There has been a reiteration of conflict of interest in all presentations, how can a regulator who partners in research also monitor?
- How we can come up with alternate structures? How do we define independence?
- We must look back in history to know what worked successfully, and where we transgressed. Moreover, this knowledge must be included in medical practice and knowledge accreditation.
Discussion Points

- Holding institutional EC members accountable is problematic as most of these members are volunteers; such compulsions inhibit involvement and compromise the character of autonomous scientific research. Focusing on institutional complexity makes it hard to establish the causal relation.

- Volunteerism cannot and should not discount the accountability of the ECs, efforts for training, registration and auditing of these committees must be put in place.

- How does the proposed Bill on Human Subject Protection in Health Research justify the fact that the CRO has a role in the public domain without accountability? Most of the research work is carried out by CROs who also assume responsibility of supervision instead of the PIs. Yet their personnel are invisible to us. In the current scenario of commercial or sponsored research, CROs are unavoidable. The alternative of public funded research may not be viable. Furthermore, the State too has been a violator in several cases.

- The statement that vulnerable groups should not be involved in the trials cannot be justified. It is akin to saying those who do not understand their rights cannot exercise them. Everybody has a right to participate and it is the responsibility of the government to create a structure that will protect the interests of the vulnerable groups.

- It is important to work within the limitations of the reality today. In a scenario, where pharmaceutical companies exercise huge power over the government and there are increasing mergers, acquisitions and collaborations with foreign companies, extreme steps become necessary. Demands must be made for a ban on CROs and Independent ECs, where the agenda is clearly profit making, if not profiteering.

- In several cases, where violations have been proved, the government has failed to take any action, the case of the HPV vaccine being the most recent. Even though this case was taken up in the parliament, no action has been taken against the culprits. It is apparent that even the making of the law is clearly driven by market forces.
The session focussed on two important issues related to the practicalities and the implementation of the systems of regulation in India today. In his presentation, Dr Sujith Chandy from Christian Medical College (CMC) Vellore, looked into the aspects of assessment, management, and compensation of AEs that may occur during the course of the clinical trials. He also talked about the various dilemmas faced by a researcher in this regard, and the loopholes in the current guidelines with regard to these dilemmas. Dr Roli Mathur from ICMR spoke about the importance of accreditation of the ECs while stressing on their role as the main monitoring body. She also elaborated on the measures taken by the ICMR to strengthen these institutions further. Ms Rohini Kandhari followed with a brief intervention of her study of the EC members and their roles, as part of her MPhil research at Jawaharlal Nehru University (JNU) on the same subject.

**Presentation I — Adverse Events in Clinical Trials: Assessment, Management and Compensation**

**Dr Sujith Chandy**

This presentation focuses on the critical areas of assessment, management and compensation of AEs that may occur during the course of a trial. There is always an element of a benefit and risk in the use of drugs, which is also translated to the methodology of clinical trials, wherein a trial is nothing but an experiment with an unknown outcome and an associated risk (expected or unexpected). Hence it is important to discuss this issue further.

**Safety Assessment**

There are different terminologies that may be used to assess the degree of seriousness of an event – Adverse Event (AE), Serious Adverse Event (SAE), Adverse Drug Reactions (ADR), etc. Understanding the difference between these terminologies is important.
For instance, an ADR is a noxious and unintended response to a drug and occurs at doses normally used in human beings. An AE, on the other hand, may be any untoward medical occurrence that may or may not have a causal relationship with the treatment. SAE may be defined as an adverse event that is life threatening, or requires inpatient hospitalisation, may result in persistent or significant disability or incapacity, or in a congenital anomaly or birth defect, or ultimately even result in the death of an individual.

The safety assessment of a drug is determined by an interplay of various factors such as assessment of causality, intensity, and resolution.

**Causality Assessment**

The greatest difficulty often stems from the inability to determine whether an event is an adverse event, and is the outcome of a particular drug. It is here that the financial strength of the industry has a major impact.

Causality of an event is determined using several criteria, and may be considered a science by itself (Figure 22). These criteria include:

- **Temporal relationship or Time profile:** The time between the taking of the drug and the occurrence of the event.
- **De-challenge and re-challenge:** Stopping/continuing the drug for a period of time to see if the symptoms disappear/reappear.
- **Objective confirmation – Lab tests.**

However, the algorithms that are used to determine causality are very varied. For instance, the World Health Organisation (WHO) uses the variations of definite/certain, probable/possible, or doubtful or unlikely. But not only is the efficiency of the science of these algorithms not yet been proven, it is also not known whether these are the best methods to determine causality during the course of a clinical trial. This is an area that needs further discussion and debate. Moreover, although pharmaco vigilance follows the WHO definition in most cases, in the case of clinical trials, assessment is done only to determine whether an event is related or unrelated to the drug administered. This, however, may result in gray areas, in false negatives.
**Reporting of an Event**

The ICMR guidelines as well as the Drugs and Cosmetics Act enlist various timelines and forms for reporting an event that may occur during the course of a clinical trial. However, there is such a large volume of clinical trials that the follow-up and monitoring of these reports becomes a major problem. Most IRBs and ECs are overworked and understaffed and find it difficult to respond quickly. Hence, there is very little follow-up and monitoring of even those events that are reported.

It is often assumed that AEs are physical by nature and involve injuries or disabilities, but it is extremely important to also think of them as having implications on the mental, economic and social well-being of a person (Figure 23).

### Management and Compensation of Injuries

**Rights, Awareness, and Responsibilities of Stakeholders**

Most of the time, potential participants are not aware of the risks involved in the trials and how these risks should be managed. Not only the participants but even the investigators are often unaware about the guidelines and the mechanisms of management of AEs.

**Treatment and Payment Issues**

While reimbursement may be given to victims of AEs in some instances, compensations are generally rare, with very few cases having been recorded. Moreover, there is an added complication as to how can death be quantified. This is a critical area that needs immediate attention. Some of the questions that need to be answered are: Is there a compensation for loss of wages and time? Is there an advance deposit by the sponsor for research related injury? In case of death, how does one determine compensation?

**Protocol and Contract**

Very often, the protocol and contracts are ambiguous and vague terminologies are used. Even though there may be a provision for compensation in the trial budget, it is often arbitrarily drawn up without any proper assessment of the risks involved. Moreover, no consideration is given to issues such as product liability; particularly in the case of global insurance, the duration of the insurance versus the trial period, assessment of long term side effects, etc.
Moreover, there is also the question of how injuries resulting from protocol deviation can be assessed and compensated.

**Risk and Compensation Assessment**

How to assess the adequacy of insurance or indemnity or compensation in proportion to the risk and the value of the loss? Can minimal risk or clinical equipoise ever be validly or quantitatively assessed? How does one estimate the compensation based on standard of living? Who is responsible for doing the assessment? Is it the sponsor, the investigator, the institution, IRB, the regulator, the independent body, or the legal body?

**Role of IRBs**

IRBs play a major role in this area, ranging from looking at preventive measures, to monitoring, advisory and curative roles in assessment, management and compensation of AE or injuries. However, a lot still remains to be done in this regard. The IRBs are plagued by issues related to member constitution, time and availability, ethical training, legal awareness, and protocol and IC review. The question here is whether the IRBs should limit their roles to monitoring and preventive capacities, or should they also assess prospective liability with independent assessors? Is it possible for IRBs to determine whether insurance, indemnity or compensation has been adequately settled?

**Additional Protection**

Some of the concerns with regard to additional protection of the trial participants are:

- Local policy of institution – hindrance or protection?
- Insurer – Indian or foreign company?
- Terms and conditions – ever given or shown to site?
- Is the injury due to fraud or negligence?
- Presence of grievance redressal committee, Data and Safety Monitoring Board (DSMB) or extra arbitration committee?
- More research in current profile of clinical trials in India.
- Clarity and strengthening of laws, guidelines and policies.
- Awareness for all stakeholders and training.
- Advocacy for participants’ rights.
- Categorisation and assessment of injuries and determining compensation.
- Death and compensation issue needs more thought.
Specific Needs and Recommendations

Following are the recommendations for carrying out the trials:

- Training for investigators in AE and GCP.
- Clinical trials must be conducted in registered institutions.
- Independent body for assessment of trials.
- Independent body for reimbursement and compensation.
- Training for all IRB members.
- Post marketing surveillance of AE – monitoring must not end with the end of the trial.

Presentation II - Role of Ethics Committees and Other Existing Regulatory Infrastructure for Clinical Trials in India

Dr Roli Mathur

Role of ECs and Regulations

Clinical trials are one of the most valuable sources of evidence of the safety and efficacy of health interventions, thus making the role of ECs extremely important. ECs are not limited to only ensuring the protection of research subjects, but are also concerned with the public acceptance, trust or confidence in biomedical research. Hence, the quality of ethical review is of prime importance.

| Figure 24 |
| Regulations & Guidelines for Clinical Trials |
| • Drugs and Cosmetics Acts & Rules (1940, 1945) |
| • Schedule Y (2005) |
| • GCP Guidelines (2001) |
| • ICMR Ethical Guidelines for Biomedical Research on Human Participants (1980, 2000, 2006) |
| • Medical Council of India Act (1956, 2002) |
| • National P.Vig Programme, 2004 |
| • BA/BE Study Guidelines, 2005 |

Responsibilities of Ethics Committees

- To protect the dignity, rights and well being of the research participants.
- To ensure that ethical values are expressed as local community values and customs.
- To assist in the development and education of a research community that is responsive to local healthcare requirements.
- To enforce all statutory and non-statutory provisions related to ethics in medical research with sound judgment and meticulousness.
- To function as per Standard Operating Procedures (SOPs).
• To maintain and archive records.
• To remain abreast of new ethical issues due to advancements in science and technology.

Setting up of Ethics Committees

It is important for all institutions involved in biomedical research or clinical trials to set up a special committee of members to look into the responsibilities of the ECs. The institution must also clearly define who the EC is answerable to. Only under special circumstances, or if the institution is not very large and does research on a small scale, can provisions be made for joint ECs. Similarly, institutions with a larger scale of research operations could have multiple committees and sub-committees. However, in both cases, it is extremely important that an appropriate policy is put into place with proper agreements to prevent any form of EC shopping. The EC review should be in accordance with national and international guidelines as specified by the SOPs, and must carry out both scientific and ethical reviews. The committee must be responsible not only for an initial review, but also for periodical monitoring for compliance of ethics.

Figure 25

<table>
<thead>
<tr>
<th>Composition of IECs</th>
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<tbody>
<tr>
<td><strong>ICMR Guidelines</strong></td>
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<tr>
<td>• External Chairperson</td>
</tr>
<tr>
<td>• One - two persons from basic medical science area</td>
</tr>
<tr>
<td>• One - two clinicians from various Institutes</td>
</tr>
<tr>
<td>• One legal expert or retired judge</td>
</tr>
<tr>
<td>• One social scientist/ representative of non-governmental voluntary agency</td>
</tr>
<tr>
<td>• One philosopher/ ethicist/ theologian</td>
</tr>
<tr>
<td>• One lay person from the community</td>
</tr>
<tr>
<td>• Member Secretary</td>
</tr>
<tr>
<td>• 8-12 members, quorum 5</td>
</tr>
<tr>
<td><strong>Schedule Y</strong></td>
</tr>
<tr>
<td>• External Chairperson</td>
</tr>
<tr>
<td>• One basic medical scientist (preferably pharmacologist)</td>
</tr>
<tr>
<td>• One clinician</td>
</tr>
<tr>
<td>• One legal expert or retired judge</td>
</tr>
<tr>
<td>• One social scientist/ representative of non-governmental organisation/ philosopher/ ethicist/ theologian or a similar person</td>
</tr>
<tr>
<td>• One lay person from the community</td>
</tr>
<tr>
<td>• At least 7 members, quorum 5</td>
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Every EC must fulfill the following requirements to ensure that it functions effectively in the highest ethical spirit:

• **Terms of reference:** for appointments, duration of trials, terms, renewal, replacements, resignation, frequency of meetings, fees, etc., defined in written SOPs.
• **Training:** Members should be abreast of latest developments, orientation courses, ethical guidelines, GCP, regulations.
• **Regulation**: There is a proposal to set up a Biomedical Research Authority under the draft ethics bill, to register all IECs, and to evaluate, monitor, and promote accountability and transparency.

• **Review procedures**: Ensure that the scientific review is completed before ethical review.

• **Secretariat to screen, categorise**: Exemption from review, expedited review, full review.

Procedures that are to be followed by an EC include:

• Submission of application: that must be complete in all respects, including all documents and checklists.

• Review process - through formal and regular meetings and not by circulation.

• Decision making - through a quorum, without conflict of interest with consideration of risk or benefit of vulnerable population.

• Periodic Review or Continuing Review or Interim Review or Monitoring must be carried out at specified intervals, and must include redressal of complaints or reported violations, site visits, etc.

• Stringent record keeping of all proceedings.

• Administration and management - a full time office with institutional responsibility.

However, there are several challenges that ECs in India face today. Clinical trials are often multi-centric (conducted at different institutions and in different countries) and display significant cultural differences across locations. There are also differences in laws and the EC should have the discretion to implement laws relevant to the particular research (in India or International). However, the established practice of local review are inadequate for assessing new technologies and methodologies, constantly raising ethical questions not anticipated by existing procedures and guidelines. Also, the set-up, structure and practice of different IECs vary considerably and there is a lack of awareness of specific working practices of IECs in India. ECs in India today, vary from being fully functional to simply existing on paper. There is also an urgent need to enhance knowledge, support review and development of opinions, and meet challenges and emerging ethical issues. ECs often have to deal with insufficient support from institutions both in terms of financial as well as moral support. Meetings do not take place as per schedule, and quite often, are simply circulated on paper. Any objection raised by these committees is frequently viewed as an obstruction to the research, and hence considered an unnecessary delay. Due to this there seem to be an increasing number of independent ECs, mostly in the private sector, with conflicting financial interests and poor quality of review.
Towards Improving Quality of Ethics Review

Review and Implementation of Informed Consent Format (ICF)

The primary role of the EC is to look into the process of informed consent by the participant of the trial. This is not merely limited to the content of the format but also to the process by which the consent has been procured. Hence, the complex nature of information, and complicated terms such as randomisation, placebos, etc., need to be simplified. The EC needs to ensure that they have the required information on the profile of the participants so that they can identify and reduce the scope of any therapeutic misconception and power hierarchies between the doctors and the patients. It is also the responsibility of the EC to ensure there is no form of undue incentives for participation, and the participant’s rights receive complete protection at all times. The EC is also responsible for reviewing some of the other tricky issues related to monetary payments, research amongst vulnerable communities, pregnant women, children, and storage of samples, etc.

Recommendations

- Community representation is important, right from designing the study to its implementation.
- Prevent exploitation due to increased vulnerability created due to social contexts of research.
- Early phases of research in communities which are less vulnerable, conducted only if necessary after putting adequate safeguards in place.
- Provisions for best nationally available care to participants.
- Burden and benefits to be equally borne by collaborators.
- Guidelines and regulations of collaborating countries to be respected and those of the host country should be followed.
- Capacity building to address issues due to collaborative research.

Positive Steps

Since 15 June 2009, trial registration in CTRI has been made mandatory by the DCGI. Many journals such as the International Committee of Medical Journal Editors (ICMJE), now accept only registered trials for publication, while the approval of clinical trials by the DCGI is subject to approval from the EC and needs to follow ethical guidelines for research. Some other activities of the ICMR include: preparation of guidelines, educational activities and trainings, creation of a webpage on bioethics, submission form and SOP templates,
draft Ethics Bill, establishment of an IEC comprising ICMR, WHO and MoU, signed for capacity building in Bioethics, etc.

**Looking Ahead**

- Setting up mechanisms for IEC registration, registration of CROs, clinical trial sites and investigators, ECs.
- Making the ECs answerable to regulators.
- SIDCER recognition was awarded to TMH & KEM Hospital, Chiang Mai, Thailand in 2009.
- GCP training of investigators by an accredited body.
- Penal provisions for violation of clinical trial regulations.
- Guidelines for SAE reporting.
- Draft guidelines on approval of clinical trials and new drugs, for conducting clinical trials with medical devices.
- Guidance on clinical trial inspections.

**The Cherished Dream**

It is important that IECs act independently, judiciously, and expeditiously. They must strive to create an environment of ethics all around, with the institution as well as with all stakeholders. This will ensure that ethical imperatives also become a part of behaviour, and not merely of regulation. The ultimate goal is to protect the interests of the human participants, thus ensuring ethically sound research. This indirectly promotes the interests of the investigators as well as of the institution.

**Intervention on Role of Ethics Committees**

**Ms Rohini Kandhari**

My intervention is drawn from the findings of a study I conducted while at JNU, and is based on the conversations I had with EC members, both at public and private hospitals. Research or studies on the actual functioning and inner workings of the ECs, are scanty.

There is very little transparency as regards the membership of ECs, and the means by which individuals are selected to be a part of these committees. There is also practically no information in the public domain, within and outside medical institutions, regarding
their motivations for joining the EC. Most often, the selection procedures are arbitrarily carried out through social networks and hierarchies within the institutions. For instance, doctors are appointed by seniors, or by virtue of their connections with an association. Amongst the committees profiled, more than half the members had other intra-institutional associations. When queried about their role in the EC, responses of members ranged from considering their role as a burden or an additional responsibility; a matter of prestige or career advancement, did not have a choice, was an obligation.

While on paper the ECs are multi-disciplinary, in spirit, this does not seem to exist. There is little room for an external non-medical member to express an opinion. The medical scientist members of the committee are the most assertive, and are the dominant voice during EC deliberations. The inherent hierarchy between the medical expert and the non-expert, and the highly technical information and protocols obstruct effective participation, as very often the investigator is also invited to present the protocol before the committee. For example, a non-medical member who fulfilled the role of a social scientist in her EC stated, “I can't ask the doctors anything. They assert their knowledge of medical technologies. It is a closed circle and at times I feel like I am not doing justice. Three of us are from outside and we don't usually say anything.”

Also, the role of the non-medical member in the committee is often underrated and is dismissed. For example, a member secretary stated that in an EC, a lawyer is required for reviewing IPR applications. An external member, a Professor of Hindi stated that he had a minor role of examining the Hindi translation of the consent form, which, although integral to the process, cannot be limited to only that aspect. Therefore, even when non-medical members, who understand the importance of their roles as non-affiliated, outside people, raise an objection, there is very little they can do.

In one extreme case, the patient died during a clinical trial. A non-medical member raised a question about the objectivity of the appraisal process by which it was determined that the death of the research subject was unconnected to the trial or the institution. The member was told that the appraisal was done by a special team of doctors. The team was in fact from the same hospital where the trial had taken place. The member felt that his objection was being misinterpreted, and was being seen as doubting the integrity of the institution and the doctors. He decided to let the matter go. From this example, it is evident that although non-medical members comprise almost half of the committee, and are meant to balance the medical perspective or counter it, they have in fact, merely an obligatory presence.
The ECs seem to be working in isolation with the trial subjects. None of the members I spoke to make any on-site visits; their ethical assessment is confined to desk review. The reasons for this ranged from lack of resources to shortage of time and staff. Member secretaries recommended that an external agency be hired to do the monitoring. But in public hospitals, no training was given to member secretaries, and in fact, two of them had not even read the ICMR guidelines.

In conclusion, it is very important to dialogue with EC members, to know their experiences. They lack administrative support, have no training, and the guidelines which are the sole instruction manual for the committee members, abound in ambiguities.

Comments by the Discussant and Chairs

**Dr Jacob Puliyel**

- The Brighton Classification of AEs\(^{11}\) categorically states that if an AE occurs after the drug or vaccine has been administered, and there are no other indications for the event, the drug will be considered as the possible or probable cause of the event.

- We are asking ECs and Institutions to assess whether the administered drug is responsible for the AE, in which case that particular institution should be liable for compensation. For example, in Sri Lanka, there was a cluster of four deaths following the administration of the Pentavalent vaccine. The WHO tested the vaccine for contamination, calculated the time relation between the time the vaccine was administered and the event. Despite these findings, the WHO classified the event as probable/possible causality, and declared that the deaths were likely to be unrelated to the vaccine. This makes one wonder whether even the WHO can be trusted, let alone the ethical bodies of the institutions conducting the trials.

- Any review board or EC, should generally inquire whether any compensation is being offered to the subjects for participating in a particular trial to check for any undue inducement. If compensation is indeed being offered, that study should be condemned as unethical for the reason of misuse of poverty and other vulnerabilities.

- Reporting an incident to the ethics bodies does not yield any results, as in most cases, they meet only once a month and sometimes not even that often. A review of what has already been presented is very seldom done, thus allowing unethical or dangerous practices to continue without being checked.

\(^{11}\) Developed by the Brighton Collaboration, an international voluntary collaboration that facilitates the development, evaluation, and dissemination of high-quality information about the safety of human vaccines. It’s primary aim is to develop globally accepted and implemented standardised case definitions of adverse events following immunisations.
Protocols are generally passed by an international institution or firm and are handed over to the CRO, who is not responsible for the ethical monitoring of the trial once it is handed over to the researcher. The researcher, on the other hand, is not adequately trained and is unaware of what is being done at other sites. Who then is actually responsible for making sure that the protocol and guidelines are followed at these multi-site researches?

Dr Vineeta Bal

It is quite insulting to assume that an illiterate person will not be able to give consent in the true sense of the word. Although poverty and literacy often go hand in hand, that should not prevent participation in clinical trials. Moreover, it is absolutely untrue that doctor-patient hierarchy and power struggles are limited to only patients from poorer sections.

Mr A.K. Pradhan

Clinical trials are important for drug development and there is no doubt that they should be conducted in the most ethical way possible.

The industry has various stakeholders and players, each of who must stick to their respective roles and responsibilities, as laid down in the guidelines and the Drugs and Cosmetics Act. There is also an urgent need to strengthen the regulation of clinical trials.

Discussion Points

While considering cultural needs and specificities in the context of ethics and clinical trials, regulation may seem to be important. But it is extremely dangerous for universal values to be given up to make way for these specificities.

An SAE is supposed to be reported to the sponsor within 24 hours, who is in turn, expected to inform all the centres/sites about this event. However, for such a procedure to be efficient, the network between the sites, which at the moment is in a state of complete chaos, with one site completely unaware of what is happening at another, needs to be well organised.

As was seen in the HPV vaccine case, the IRBs had not met for several months on end, with no consequences whatsoever. How does one hold ECs and IRBs accountable in such a case – what does this mean in practical terms?

In case of occurrence of SAEs at different sites, it is mandatory to inform the IEC; such a collective causality is practically non-existent since it is very time consuming.
At present, all such events are dealt with by the sponsor, who discourages the PIs from documenting the SAE on record, and instead sends the victim to a public or low cost facility. Regulatory authority interventions have also never been witnessed in such instances. There is a lack of clarity regarding the mechanisms required to respond to these events, and an urgent need to come up with strong guidelines to address issues of compensation and management of AEs, including those related to ECs.

- Lot of discrepancies have come to light regarding the CTRI. These include lack of site addresses, lack of information on ECs and their constitution, removal of sites without prior notice. Although this registry has been created, there is no monitoring of the information entered in the registry. Such an exercise will have to be undertaken by a public body given the scale and scope of the database, making it impossible for a lay person to do so.

- When information comes to the regulators, what is their responsibility for follow up? Can we simply depend on standards – or is it not, in fact, the role of the regulatory authority to take the initiative to follow up and take necessary action.

- Over the last decade, since the finalisation of the ICMR guidelines, it is now time to question whether the ICMR has ever reviewed the whole concept and structure of ECs. The very structure or framework in which these committees operate is entirely voluntary and yet they carry the entire burden of monitoring. This is a system that needs to be reworked from scratch. There is no point in discussing these issues and new guidelines on ECs, if the framework itself is proven to be unworkable.

- It is important to ask the question as to what the role of the DCGI is. Also, what regulatory authority does the DCGI have in a scenario where everything related to patient safety is being outsourced to the IRBs and ECs? Are the guidelines used by the DCGI at the stage of reviewing of applications for licensing of clinical trials? Is the application reviewed for scientific value or social relevance?

- A constitutional body like CDSCO, with an allocated budget in its mandate does not seem to worry about the safety aspect of a trial at all, while an EC – not created by law nor with any form of public funding, completely at the mercy of the institution, with no power of any kind, is expected to carry out these tasks.

- Where are the reports of the ICMR’s surveys on ECs? If ICMR is laying down guidelines for ethical conduct, there is an urgent need for an ethical introspection within. Why are there only two accredited ECs in the country, especially in view of the fact that the ICMR itself has 30 IECs; why are none of these accredited? A change in these procedures will open up the industry to better ethical review. If the house is not put in order now, there will be an even louder public outcry in the future.
During the first session of Day II of the consultation, Dr Kaushik Sunder Rajan from the University of Chicago, explored the political economy of biomedical research in India and proposed a structure steeped in the ideals of public health to understand and respond to the current crisis in clinical research. Mr Vishwas Devaiah, from the National University of Juridical Sciences (NUJS), focussed on patents, intellectual property rights (IPR), and the lack of transparency in the industry today, that severely affects access to drugs for post trial participants as well as the society at large.

Presentation I — Surplus Health, Clinical trials and Access to Medicines: Structural and Conceptual Provocations

Dr Kaushik Sunder Rajan

I am as concerned with the question of clinical trials and the exploitation therein, as all of you are. However, I am always nervous about moral positions, including ones that I am in broad sympathy with. Hence I will attempt to elucidate the structures within which global biomedicine becomes exploitative. It is important to understand the structural contexts and contours since a response based on moral outrage will at best be ineffectual because it will always be responding to scandal, and not actually transforming the structures under which exploitative systems perpetuate; it will at worst be harmful, because these contexts can end up policing and inhibiting legitimate and important research activities.

Through my presentation, I will attempt to examine the structures within which the political economy of biomedicine is shaped and formed in order to set up an argument for the terrain within which policy and political battles need to be fought.

I will base my talk on three fundamental arguments, or take home messages:

1. We cannot understand contemporary biomedicine unless we understand the process by which health itself has come to be appropriated by capital. In other words, we cannot afford to base our battles on an argument for health, because health in the
context of global biomedicine is very different from what we intuitively think and care about as health.

2. This apparatus of global biomedicine brings up critical questions regarding the imperial dimensions of contemporary biocapital; therefore any response has to ground itself in postcolonial politics. However, it would be interesting to think about what postcolonial politics without nationalism would look like. In other words, what a postcolonial response to global biocapital would be that does not fall back on the age old ‘us vs them or ‘this is in our national interests’ argument. I feel that such positions preclude the possibility of the all-important solidarity-building that needs to happen between patient and civil society communities worldwide.

3. It is important to think about the globalisation of biomedicine in relation to not just markets and value, but also to knowledge as there is a knowledge politics at stake here, especially, in relation to evidence-based medicine.

In my presentation today, I will attempt to explain, simultaneously, the capitalisation of health; the imperial dimensions of this capitalisation; and its consequences for knowledge politics and evidence-based medicine. I will argue in favour of socialisation of health; a postcolonial, but global, non-nationalist, political and policy intervention; and the extension of the biomedical research apparatus to rigorously contextualised concerns with policy.

**Part 1: Capitalisation of Health, its Imperial Dimensions, and Structures of Crisis**

The field of drug development is configured in such a way that multiple actors manage to be in crisis simultaneously. This is a consequence of three structural and historical shifts. The first is the appropriation of health by capital. The second is the increased salience over time, of speculative capital determining the ways in which capital-intensive drug development gets valuated. The third is the recent globalisation of these appropriative and speculative logics.

I will begin by focusing largely on the Euro-American multinational pharmaceutical industry, which is involved in research and development (R&D) based drug development. This R&D driven pharmaceutical industry operates in a scenario marked by high drug prices. These prices are justified by the enormous cost and risk of the drug development process, and they are made enforceable by patents and other allied forms of monopoly protection. The following are the factors that come together to configure the fundamentals of the market of pharmaceutical development.
In the 1980s, the pharmaceutical industry began to focus on R&D driven business models, leading to the development of ‘blockbuster’ drugs that could earn over a billion dollars in annual revenue; second, the regulatory infrastructure in which larger and more complex clinical trials were mandatory before drugs could be approved by market became increasingly elaborate; and lastly, the emergence of the possibilities of biopharmaceutical development\(^\text{12}\). These were often based on a more precise and mechanistic understanding of the biological functions rather than the earlier generations of drugs that were developed largely through random screening of natural products, and trial and error.

In the 1990s, a couple of significant developments occurred that contributed to the shift in the pharmaceutical industry. A Tufts University study revealed that the price of developing a new drug was of the order of $250 million dollars. While these figures are almost certainly inflated, what one sees through studies such as this is that the calculus of drug development costs becomes a central part of the discussion on the relationship of drug R&D and drug pricing. The second feature of the 1990s was the pioneering of off-label use\(^\text{13}\) as a business model.

Over the past 30 years, along with these changes in the business models of pharmaceutical companies, there has been a progressive movement of clinical trials into the private sector. Further, in the mid-to-late 1990s, trials were moved out from the US, to the rest of the world at a rapid rate. By the turn of the century, the contours of the pharmaceutical industry had changed dramatically. It was a large industry that was extremely profitable. But these were profits that were built on the strength of a handful of blockbuster drugs, molecules that made in excess of a billion dollars a year. These drugs offset the high rate of failure of other drugs that did not make it through clinical trials (probably four drugs out of every five). Hence, this was an industry whose profits, although huge, depended upon a large amount of money from a small number of compounds. The ability to make so much money from these compounds was secured through monopoly, primarily through strong intellectual property protection.

There are three factors that make this configuration a structure that is potentially ridden with crisis: the place of the pharmaceutical industry in the speculative marketplace; pipeline problems; and the patent cliff. Most major R&D driven pharmaceutical companies are publicly traded. This means that value for these companies is determined less by profit (how much money they actually make over the amount expended) than by growth (how much

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\(^\text{12}\) The development of complex biological molecules as drugs, as opposed to small organic chemical, molecules.

\(^\text{13}\) Involves selling a drug for an indication other than that for which it was initially approved.
potential there is for future earnings over and above the present rate of earning, which can be translated into shareholder value). If only 1 in 5 drug candidates entering clinical trials makes it to market, then in order to generate 3-5 new chemical entities a year, one needs a large number of drugs entering the clinical trials pipeline. However, the absence of a robust pipeline in the pharmaceutical industry results in a crisis. The pharmaceutical industry has, at least since the mid 1990s, faced what is referred to in the industry as an ‘innovation deficit’. The crisis of the pipeline exacerbates the already existent structural crisis because of the relationship between the pharmaceutical industry and the speculative marketplace.

In this situation, the one thing that saves pharmaceutical companies is the handful of blockbuster drugs that make more than a billion dollars a year. The only way these drugs have been able to make so much money, however, is because they are protected by the monopoly afforded by the patent. Hence, intellectual property becomes the critical factor that allows value generation in this business model. This is where the phenomenon known in industry circles as the ‘patent cliff’ becomes a potential source of crisis.

The pharmaceutical industry is in crisis from both directions – the looming expiration of patent monopolies on currently profitable drugs, and the lack of an adequate pipeline of new drugs to replace those that will start facing generic competition upon patent expiration. This leads to certain changes within the business strategies of pharmaceutical companies, especially the recognition of the importance of near-term revenue; there is a greater focus on mergers and acquisitions (M&A) rather than on R&D.

The very definition of health comes to be at stake and reconfigured in this process. What one is seeing now, is the implicit understanding of health in terms of what Joseph Dumit has referred to as surplus health. This is where health itself becomes abstracted from healthiness and operates purely as a potential for the generation of surplus value, in the manner that labour does when it becomes surplus labour in industrial capitalism. If health is not valuable, pharmaceutical companies will not invest on R&D. This is why, simply making a moral argument about pharmaceutical companies not being innovative, or not researching neglected diseases, or not making drugs accessible, is not good enough – one has to understand and intervene in the structural and systemic factors that lead these companies to act in this way.

**Structure of Crisis for Patients**

At a basic, conceptual level, the pharmaceutical industry, over the past thirty years, has resolutely shifted away from being in the business of healthiness to being in the business of health, where health itself gets redefined into becoming something alienable and
appropriable, a source of surplus value in a manner analogous to that by which labour became surplus labour under logics of industrial capital. Patients, in this equation, have no meaning except as potential future consumers of therapy.

If one is considering an industry that operates within a value system that is fundamentally dependent on market growth, then one has to also consider the various ways in which markets can be potentially grown. One way for a company to grow its market is to come out with a new therapeutic molecule, but this is time consuming, expensive and risky, and has not been as successful over the past decade as capital markets require. A second way is by expanding the indications for medications on the market through off-label use, or to reframe diseases as chronic or requiring prophylactic and preventive intervention, which is the mechanism of surplus health generation that operates most strongly in First World markets. A third way, in principle, is to expand markets into emergent markets. This is harder to do for the pharmaceutical industry, because of its concerns with protecting intellectual property, and maintaining control of their ability to set prices. Therefore, including developing country populations within a global market calculus, while attractive, has its limitations.

However, value can be increased if the price of drug development is reduced. This is best achieved by reducing the cost of the clinical trials process by outsourcing the trials to the developing world. This does not require the developing world to be constituted as a market; one does not need to sell a drug in a country in which one tests a drug.

In this context, there are two ways in which India has become incorporated into the globalisation of drug development since the mid 1990s. The first one is related to the globalisation of clinical trials, and the second concerns the global harmonisation of intellectual property regimes under WTO.

India is a potentially attractive destination for clinical trials, because of the presence of low-cost, bioavailable experimental subject populations, combined with good quality medical infrastructure. These logics of bioavailability, where Indian subjects are not consumers but, 'labouring bodies in circuits of biocapital', are also seen in the ways in which India has been emerging as a global destination for surrogacy. The parallels between clinical trials economies and the economies of global reproductive politics are essential to think about here. But there is also the fact that India is a country with a burgeoning consumer class, and constitutes an emerging market of enormous potential. Hence, there is a desire to include India into a global pharmaceutical market. It is pertinent to note the contradiction here.
A stringent intellectual property regime, which is what these companies now have post-WTO, limits how much countries like India can be imagined as markets at all, since this necessarily leads to the pricing of many patented therapeutics beyond the reach of many Indian patients.

India’s entry into surplus health economy also means that it puts the Indian generic industry in crisis. Indeed, larger Indian companies have emerged as attractive acquisition targets for multinational pharmaceutical companies. This is not least because of their generic capabilities that are potentially attractive to leverage for revenues by acquiring companies in post-patent cliff scenarios in the West. Hence, Indian companies are moving from being manufacturers of bulk drugs as commodities for sale in Indian markets, to becoming outsourced manufacturing facilities for multinational pharmaceutical companies. What I have done so far is to try and provide a schematic rendering of this political economy of the pharmaceutical industry.

But any adequate critical and political response to this crisis has to come with the understanding of the ways in which health itself has come to be redefined through its appropriation by a globalising, speculative capital. Therefore, it has to insist upon a structure and institutionalisation of a form of health that resists such appropriation.

I would like to end my presentation by making some thought-provoking suggestions in terms of what this structure of crisis means, and responses to clinical trials and drug access.

The first point that I would like to emphasise is banal, but perhaps important. Part of my attempt to understand the pharmaceutical economy in structural terms is so that I can resist making simple, agential attributions of mal-intent to pharmaceutical companies. There is no question that the entities involved in the institutional apparatus of global biomedicine have to be held accountable, and that the actions of some of these entities do invite moral outrage. But by understanding the constraints within which these companies operate, we can understand how they are in fact captured by certain logics of capital; it does not make sense for them to operate differently from the way they do.

If we are thinking of legislation, then, it cannot simply be at the level of regulating the entities involved in clinical trials or pharmaceutical development, it has to involve transforming the political and economic structures within which these processes occur. One of the difficulties in doing so has to do with the almost cognitive impossibility, today, of imagining a world outside of capitalism. I am not arguing for a return to communism,
but I am insisting that we have to think seriously, about what socialisation of health might imply for our contemporary political reality, and how this socialisation can be legalised. Thinking about ethics and regulation in the absence of structural transformation is, at best, a holding operation. One place to begin this transformation might be the insistence of a nationalised health care system. Another place to start might be to think about what it would take to rejuvenate a public sector national pharmaceutical industry.

My second point is that although access to drugs and lack of exploitation are necessary, they are not sufficient in thinking about institutional and regulatory regimes for clinical trials and therapeutic access. Even nationalised health systems can result in systems of exploitation, therapeutic saturation, and crisis, unless we can think beyond pharmaceutical solutions to health problems. Joao Biehl and Adriana Petryna describe how patients are suing the Brazilian government for inaccessibility of medicines. They alert us to the ways in which the struggles for access to essential medicines in Brazil have led to a natural correlation between public health and pharmaceutical therapy.

Firstly, this puts an enormous burden on the State’s resources to provide healthcare to its citizens. Secondly, it ends up bypassing the concern with evidence-based medicine; pharmaceuticals are seen as an entitlement of the citizen, and citizens are empowered in making demands for these therapies, regardless of whether it is medically necessary for them or not. There are fine, and deeply ethically charged lines between therapeutic access and therapeutic saturation.

The third and final provocation I want to make is related to the HPV vaccine studies conducted by PATH. On the one hand, as the Sama report details, the HPV case seems to be an utterly outrageous example of a clinical trial (or ‘demonstration study’, as they call it) conducted wrongly. Questions can be asked about the purpose of the trial, the inclusion and exclusion criteria that allowed tribal girls to be experimented upon, the ambiguous nature of the ‘demonstration study’, the improper procedures followed for obtaining informed consent, etc.

On the other hand, in the context of a justice argument, there are many things about the HPV trials that are not that far, in principle, from what we are fighting for. We argue about the corporatisation of health; here, one sees the State in partnership with a non-profit organisation in a public health programme; we talk about poor distribution of biomedical innovations; here, one sees a study that is constructed to test distribution mechanisms.
Indeed, while we complain about the inclusion of vulnerable tribal girls in this study, one could imagine an alternative where the study was only done on urban populations, and it showed itself to be highly effective. We might then have complained about how effective biomedical interventions only focus on the urban elite and never reach marginalised populations.

So for me, HPV is not interesting because it shows all the things that can be done wrong; it is interesting because it demonstrates the potentially tragic consequences of ventures (however poorly implemented) that have a stated rationale of public health and distributive justice in their conceptualisation.

One of the things that is most problematic about the HPV trials is the way in which the vaccine has been touted as a vaccine for the prevention of cervical cancer. The results of post-marketing studies, however, indicate that this vaccine is effective only against two strains of HPV, and that actual cancer prevention is far more effectively done through screening programmes and other primary health interventions. The fact that the government could imagine the dissemination of the vaccine as part of a public health programme without ensuring the concomitant dissemination of a larger public health apparatus is amongst the most troubling aspects of this case.

There is a common thread between the strategies adopted around HPV vaccine distribution and the case of Brazilian patients suing the Government for access to medicines. Both presume a technocratic solution to the problems of health, and in the process, the importance of evidence-based medicine is itself trivialised.

In conclusion, I would like to say that we have to imagine what socialisation of health would look like. But the Brazilian and the HPV case, which, both in their own ways are examples of a certain kind of socialisation (albeit partial), show that simply socialising health is not enough, if we continue to think of health as something that is attainable simply through technocratic means.

**Presentation II — Intellectual Property Rights and Clinical Trials**

*Mr Vishwas Devaiah*

This presentation will focus on trying to capture those elements in the clinical trial industry that are playing havoc with access to medicine. I will look at how clinical trials are being conducted, and why it is so difficult to get information from regulatory authorities with regard to clinical trials. I will examine IPR in the context of patents and data protection, or exclusivity. I will also touch upon non-disclosure and confidentiality clauses, and attempt to map these in the context of ‘gag clauses’ or ‘gag orders’.
**Intellectual Property**

Patents or IPR originated in the investment market in medieval England, and were the privilege of some to ensure a training to bring in more investments from outside the country. The Indian patent law prior to the TRIPS agreement, however, had a different orientation of sorts, thanks to Justice Iyengar, who made tremendous efforts to modify patent laws to conform to Indian requirements. He proposed a patent system which restricted the term of the patent to a fixed number of years, particularly with respect to pharmaceutical patents. A distinction was also made with regard to process and product patents, wherein process patents were allowed while product patents were not. As a result of the efforts of the Iyengar committee, which later translated to the Patent Act of 1970, there was a robust growth of the domestic pharmaceutical industry within India, which led to a reduction in the cost of medicines, while at the same time increasing access to them. However, the downside of such a system was the lack of incentives for innovation, since domestic companies relied largely on foreign pharmaceutical companies to come up with innovative drugs.

Post 1995, India entered the TRIPS agreement, and had to cater to the demands of the WTO. By 2005, not only was the patent term extended to 20 years, but it was also approved for product patents including pharmaceuticals. Not surprisingly, in the same year, amendments were also made in Schedule Y of the Drugs and Cosmetics Rules, which permitted concurrent trials in India.

**Impact of Patent Law in India**

While the first to get affected by the patent law is no doubt the price of the drug, however, the impact is not necessarily limited to merely this price deregulation. With the new law, the innovator or originator company or patent owner will perhaps have control over how the invention is used, mainly through further licensing, and bringing in other clauses such as the ‘grant-back clause’. The grant back clause basically requires licensees to grant back all down-stream improvements, data generated through experiments, research, and any other activity that uses the invention to the patent owner, thus preventing any further down-stream research. However, it also adversely affects post-trial access to new drugs. Also, the pharmaceutical companies are constantly pressurising the government to extend the patent terms beyond twenty years.

**Non-Disclosure Clause**

The non-disclosure clause basically states that any information gained during the process of drug development or testing cannot be disclosed. A clinical trial agreement may not always have a non-disclosure clause, but it could come up in other forms of agreements such
as mergers and acquisitions, joint ventures, collaborations, etc., within the pharmaceutical industry. These clauses play a major role in determining how much information should be released to other parties, and how much is withheld. This could include all technical know-how, or only specific aspects related to the new chemical entity or drug formulation. The obvious intent is to prevent disclosure of information to competitors or third party. Any disclosure is considered as a breach of contract and the individual or institution can be held legally liable with a collapse of ‘image’ within the industry, for example, when CIPLA got into a collaboration with the Cuban government to develop a molecule for Malaria, the non-disclosure clause was one of the key clauses put in by the Cuban government along with other conditions that CIPLA was supposed to comply with.

**Confidentiality Clause**

Confidentiality in a biomedical sense is generally related to patient data, but in the true sense of the term it means the confidential and proprietary information of the company and includes (taken from a clinical trial agreement):

(i) All information disclosed by or on behalf of a company to research institutions, PIs or other research institution personnel, including without limitation, the study drug or device, technical information relating to the study drug or device, all pre-existing intellectual property of the company, and the protocol.

(ii) All information pertaining to study enrollment, status of the study, communications to and from regulatory authorities, the regulatory status of the study drug device, and study data and inventions.

Research institutions or companies or PIs or any other personnel connected with the study shall not:

(i) Use Confidential Information for any purpose other than the performance of the study.

(ii) Disclose confidential information to any third party, except as permitted by this agreement, as required by the law or by a regulatory authority, or as authorised in writing by the party to this agreement.

Thus, it is only if the regulation mandates a revelation of the information that is specific to the regulator, and not necessarily to any other party, can it be done. In case a third party needs this information, a specific permission is required in writing, by the proprietor of the information. Thus to protect confidential information, research institutions agree to:

- Limit dissemination of confidential information to only those personnel having a ‘need to know’.
- Advise all personnel who receive confidential information, of the confidential nature of the information.

- Use reasonable measures to protect confidential information from disclosure.

The parties also generally acknowledge and agree that ‘study data’ that is not published, presented, or otherwise disclosed ‘unpublished data’ remains within the definition of ‘confidential information’, and research institutions, principal investigators and their personnel do not disclose it to a third party.

Way Forward

- Patents are not rights but privileges granted by the government to bring out innovations for the benefit of the public. In the context of clinical trials, any data generated through trials should be looked at in the context of public welfare.

- There should be government funding, or prize funds to encourage innovation and clinical trials of medicines.

- The data generated by innovators should either be compensated, or treated ‘as for a public good’.

- Open source models of innovation and drug development, wherein costs and profits are shared, must be encouraged.

Comments by the Discussant and Chairs

Dr Satyajit Rath

- The political economy of biomedicine needs to be kept in mind when we think about strategies of alternative approach to public health perspectives of clinical trials. One cannot compartmentalise responses without considering the efficacy of the response.

- Drug development or non-disclosure clauses - the whole idea of the patent is to reveal information. Drug trials are carried out on patented drugs, then why is there an obsession with hoarding information? The answer to this question is perhaps linked to the commercial interests of the company, where the potential for future growth is the larger parameter that is applied, and therefore we want to keep secrets from the speculative markets and reveal them strategically.

- The rules related to patenting can be modified to provide that full disclosure is essential and trial data cannot be kept secret. Modification of the rules does not require a change in the Patents Act itself. It is possible to argue that if a drug is patented, any investigations post-patenting should not require secrecy clauses. By inference, these clauses are not related to the 2005 patent regime and can be dealt with independently.
• We need to make a clear distinction between clinical research and drug trials. In fact, the ICMR guidelines also do not make this distinction. However, most of the epidemiological researches involve human subjects. In that context, the political economy of these researches might have different implications from drug trials. To treat both of them with one broad regulatory brush is a fundamental error.

• We have not defined the public interest value of clinical trials and experimentation, and drug trials. Do we consider drug trials to be a necessary evil, to be conducted in a restricted manner, or do we think that drug trials have the potential for public welfare? It is as important to figure out how to promote the positive aspects of the trials that help the society, instead of worrying about the stray bad incidents. If we do not do this we simply limit ourselves to ‘fire fighting’.

• India has an enormous potential of human capital, however we have an equally massive deficit of trained and quality human resources. Often, it is this incompetence that leads to accidents. Therefore, any regulatory regime that requires high numbers of human resources may fail due to sheer incompetence.

• There is a need for a more diversified portfolio of responses as compared to the range of issues, in the regulation of clinical trials.

**Dr Nandini Kumar**

• Universal principles of beneficence, autonomy and justice must be applied to all clinical trials conducted worldwide. However, autonomy is often relative and sometimes requires a degree of cultural specificity to be defined. For instance, there are certain kinds of research that cannot be conducted in our country due to the cultural norms of particular communities.

• The ICMR guidelines can only provide broad parameters under which research should be carried out in India. Ultimately, things vary according to the nature of trials and the profile of the participants. For instance, during the HIV vaccine trials, an arbitration committee was set up to look into issues of compensation and AE management.

• Even though the role and responsibilities of the ECs may be quite substantial with respect to the nature of the trial, the onus of accountability continues to rest with these committees.

• While it is important to place all reports in the public domain, what is far more crucial is the follow up and action taken on the basis of these reports. The responsibility for this lies with the government and the civil society members. We need follow up and monitoring mechanisms that are sustainable.
• The setting up of CTRI and the provision for the training of large numbers of investigators and EC members have been steps in the positive direction.

• Post-trial access can become a reality in case of oncology trials if ECs intervene and insist upon it. For instance, the pharmaceutical company, Eli Lilly provided lifelong access to the trial participants for pernicious anaemia.

• There is very little quality research being done due to incompetence and lack of qualified human resources.

**Mr A.K. Pradhan**

• In the arena of new drug development, while new molecular discoveries are drying up, there are a number of blockbuster drugs that are going off patents. There is also an exponential rise in the cost of new drug development. A major concern in this regard is the acquisition of Indian pharmaceutical companies by international firms.

• It is a challenge for the government to take necessary steps to make these drugs accessible and affordable to the public, and to ensure drug security.

• There is a need to deliberate in larger forums to come up with strategies to face these challenges.

**Discussion Points**

• At the end of the day, clinical research should be carried out for public good. Clinical research is not restricted to development of drugs, but in fact, lies within the ambit of the people’s health movement. There is a huge demand for further research moving beyond drug development, and towards health systems and promotion of public health. However, unfortunately, today a bulk of financing is used for drug development.

• Moral outrage is important if we need to question and fundamentally challenge the structures within which research is done and the politics of health is played out. We need a large number of believers and not simply a small proportion of specialists.

• Perhaps it is possible for the DCGI to acquire the power to question confidentiality clauses, and modify the content of agreements with drug companies.

• Increasing corporate influence and the rise of bigger players with autonomous powers, has led to a diminished public voice across a range of issues including healthcare, policy making, and regulation. The answer to this problem may lie in political activism and the civil rights movement.
• In principle, patents are made to tackle innovation deficits. However, there is an urgent need to understand why despite the growing number of patents, there is a deficit of innovation and techniques. Is this being discussed amongst the players of the industry, and if so, what is their response?

• One of the reasons for the existence of an innovation bottleneck today is that out of the 20,000 plus human chains that are known, less than 500 are currently targeted for drug development. The bulk of these comprise enzymes. New drug discoveries by pharmaceutical companies focus on enzyme blockers, as there is a general sense that they work better. As a result we have a very small number of targets on which only a certain set of potential molecular designs are being tested by pharmaceutical companies to discover new blockbusters that are only marginally different from the existing ones. Anything outside of this is looked at as a high-risk research investment by the pharmaceutical industry, albeit without any real evidence.

• One way in which this innovation bottleneck can be tackled is for civil society to argue for public ownership of clinical trials and the process of drug development, and to seek public sector efforts that are qualitatively different from those of the pharmaceutical companies.
This session on governance, provided a platform to take a closer look at and develop a deeper understanding of four important case studies of violations in the context of clinical trials. These presentations reflected the ground realities vis-à-vis clinical trials and reinforced the concerns that had been articulated in prior sessions. While the presentations by Mr Parsottam Parmar from Raah and Ms Rachna Dhingra from Bhopal, provided an overview of how vulnerable populations are specifically targeted for clinical trials, the presentation by Dr Anand Rai from Indore, was about trials that despite being outright illegal and unethical, were approved and carried out in a government college. The presentation on the HPV vaccine project by Ms N. Sarojini from Sama, described the complete collapse of governance and regulation structures. Lastly, Dr Román Pérez Velasco from Health Intervention and Technology Assessment Program (HITAP) in Thailand, presented an alternative scenario to vaccine policies and clinical trials.

Presentation I - Clinical Trials in Ahmedabad: Ethics, Issues and Concerns

Mr Parsottam Parmar

The information I share through this presentation is based on my experiences in the field and not on secondary literature. I work in the slums of Ahmedabad and my presentation is derived from personal interviews with the participants of clinical trials.

Clinical trials in Ahmedabad are largely done on participants from poor and low income groups, particularly slum dwellers. Participants chosen by CROs are generally required to stay at the institution for a period of 2-10 days, and are given a remuneration of Rs 5000-10000, depending on the nature of the trial. The reasons for participation are many and varied. For the youth, the remuneration represents easy money for spending on things like motorbikes, mobiles, clothes, etc. For some others, the money comes in handy for paying off debts, or to meet the expenses of social functions within the household such as weddings, funerals, religious festivals, etc. Some people use the money to cover education and living costs, or to get access to medicines that would otherwise be unaffordable. Potential participants are generally approached by clinical trial ‘agents’ in the bastis/slums at night.
They are informed about the remuneration and what is required of them. No information is given about the possible risks or side-effects. These agents are generally people, who have participated in earlier trials, and have been offered a certain incentive by the CRO to recruit more participants. Land grabbing and slum demolitions have added to people’s economic difficulties, and this coupled with the loss of jobs and livelihoods have resulted in such ‘alternative’ jobs.

Some of the side effects that participants have faced include social stigma, health risks, and weakness, resulting in loss of work and wages. Given below are some of the case studies of violations that have occurred in the bastis I work in.

*Naresh I. Nadia Hatkewar,* age 28 years and married with three children, was a labourer in a plastic factory in Ahmedabad. He was a regular participant in clinical trials, which were a means of supplementary earnings for him. He last participated in a trial for an unknown disease. Soon after the trial, Naresh suffered paralysis for over a month. Since then, he has recovered partially, but has lost his voice permanently.

*Mongiben Vanker,* age 48 years, has four children and was a construction labourer. She had participated in several trials. The last trial she participated in was for some sort of cancer medication. Fifteen days after the trial, Mongiben died. Neither did her family receive any compensation, nor was any follow-up done; the rest of her family continues to participate in clinical trials to earn some income.

*Vinod Parmar,* a 26 year old taxi driver, participated in six trials. He was last recruited for a trial for an unknown tablet. He developed high fever after taking the tablet and died within three days. Once again, no follow-up or compensation was given to his family.

In another case, 45 young boys from the *basti,* in the age group of 20 to 30 years, participated in a trial for an ‘immunity reduction’ tablet. All of them suffered from high fever and cold for many days following the trial; some of them continue to suffer even today.

These cases reflect violations of the worst kind and display a complete lack of ethics. There is also a gross violation of the health and the rights of these participants as they have no access to follow-up, compensation, or rehabilitation, etc. How do we ensure that their right to financial remuneration is protected? Should the pharmaceutical companies, agencies, government departments, etc. not be fulfilling their duties? Transparency and accountability are of utmost importance to ensure that these trials are carried out in an ethical manner.
Presentation II - HPV Vaccine ‘Demonstration Projects’ in India: The Collapse of Governance, Law and Ethics

Ms Sarojini N

I am going to look at the HPV vaccine trials in India, with special focus on the post-licensure operations research, or demonstration projects. Through my presentation, I will attempt to highlight the systematic collapse of the very structures and ‘virtues’ of governance, law and regulation, and ethics, which we have been deliberating over the last two days.

To give a brief background, two HPV vaccines, Gardasil by Merck and Co. Inc., and Cervarix by GlaxoSmithKline are available in the private market in India. Gardasil was approved following a ‘Phase III trial’ in which the vaccine was tested for ‘safety, tolerability and immunogenicity’ in ‘healthy females, from 9 to 15 years of age in India’. It was conducted on 110 girls, and was completed in February 2008. Cervarix, on the other hand, was approved on the basis of a Phase IIIb double-blind, randomised controlled study, to evaluate the immunogenicity and safety of the vaccine and was conducted on 354 ‘healthy Indian female subjects aged 18–35 years’ and completed in November 2007. Interestingly, the terms ‘Phase IIIb/bridging studies’ do not appear in the Drugs and Cosmetics Act at all. Both vaccines were licensed in 2008 following these Phase III trials.

The Demonstration Projects

The state governments of Andhra Pradesh and Gujarat, in association with the ICMR and Program for Appropriate Technology in Health (PATH), launched a vaccination programme ‘against’ cervical cancer. This programme has been variedly described as a ‘demonstration project’ and ‘post-licensure operation research study’. Since 2006, as part of a four-nation initiative against cervical cancer, PATH has launched ‘demonstration projects’ for HPV vaccines in Peru, Uganda, Vietnam and India, using a grant of $27.8 million from the Bill and Melinda Gates Foundation. The vaccines, however, were provided free of cost by the two pharmaceutical companies involved, thus indicating a blatant conflict of interest.

The HPV vaccine, Gardasil, was administered to 13791 girls between the ages of 10 and 14 years in three mandals – Bhadrachalam, Kothagudem and Thirumalayapalem – of Khammam district in Andhra Pradesh, during the period July 2009 to January 2010. On 13 August 2009, the Gujarat government launched a two year ‘Demonstration Project for Cancer of the Cervix Vaccine’ in three blocks of Vadodara District – Dabhoi, Kawant and Shinor – to administer three doses of the HPV vaccine Cervarix to 10259 girls between 10 to 14 years. Prior to these ‘demonstration projects’, PATH had conducted a ‘formative research’ that was ‘designed to guide the development of a vaccine delivery strategy,’ a
communications strategy (for outreach to communities), and an advocacy strategy (for outreach to policy-makers). These projects were not registered in a public registry, nor was any information regarding the trial protocol, ethics review and other details, made available in the public domain.

The Controversy

Following reports of ethical violations and the death of six girls post-vaccination, a team of women’s rights and health activists visited one of the project sites (Bhadrachalam in Andhra Pradesh) in March 2010, to conduct a fact-finding investigation. The investigation revealed that the ‘demonstration project’ was a calculated, multilevel violation of all existing protocol on clinical trials, and a gross breach of child rights. Ms Brinda Karat, who visited the project sites, also raised the issue in the parliament. As a result of this outrage by health rights as well as women and child rights activists alike, the MoHFW suspended the demonstration projects on 7 April 2010. An Enquiry Committee to investigate into the ‘alleged irregularities in the conduct of studies using HPV vaccine by PATH’ was set up by the MoHFW. The Committee finally submitted its report to the Parliamentary Standing Committee on Health and Family Welfare almost a year later, in April 2011. While the report identifies several deficiencies in the planning and implementation of the project, it fails to fix responsibility on any individual or agency for the same. Rather than suggesting any punitive or disciplinary measures, the report identifies no ‘overt mal-intention’ and terms the deficiencies ‘minor’.

What were the ethical issues in these trials? A fact finding visit by civil society and the Ministry’s Investigative Committee’s report came up with the following findings:

Ambiguous Nature of the Projects

In an update posted by PATH on their website (accessed on 15 February 2011) following the suspension of the projects, they state:

“It should be noted that the post licensure observational studies in Andhra Pradesh and Gujarat do not seek to evaluate the efficacy or safety of these licensed, approved HPV vaccines. No biomedical outcomes are being researched; no blood or other samples are being drawn, and no therapies are being tested. The safety and efficacy of these vaccines have been documented in numerous studies and endorsed by numerous international and national regulatory agencies.”

In marked contradiction to the official stand of both PATH and ICMR, the Investigative Committee’s report states: “…4 of the 5 primary outcome measures proposed in the study relate to evaluation of the safety of the vaccine.”
Similarly, in response to an RTI application (dated 21 July 2010), Mr A.B.Ramteke, Joint Drug Controller (I), clearly stated that the design and purpose of the study was:

i) to demonstrate suitable vaccine delivery strategy.

ii) to raise community awareness.

iii) to build the evidence base of vaccine delivery strategy for future introduction of HPV in India.

However, nowhere does it mention that the outcome of the study was to evaluate the safety of the vaccine. This reveals the inconsistencies in the literature (regarding the nature, aims, and outcomes of the projects), available in the public domain. Moreover, if the safety of the vaccine was in fact being studied, it may be inferred that the projects are clinical trials.

**Choice of Location: Bhadrachalam**

Bhadrachalam (Block) one of the sites of these projects in Andhra Pradesh, is an extremely remote and largely tribal area (with a 28 per cent tribal population). The people of this area grapple with a range of problems, including loss of livelihood resulting from large scale deforestation, and regular floods, with the situation likely to worsen as a consequence of a proposed dam on the river Godavari that runs through the area. The municipality of Bhadrachalam borders Chhattisgarh, and is faced with a huge inflow of internally displaced, mostly tribal families and children, as a result of the ongoing conflict in the area. This has resulted in constant surveillance and increased vulnerability of the population. Children suffer from a range of health problems linked to poverty, lack of access to nutrition, and absence of health services. The area also has a high incidence of malaria, dengue, diarrhoea, and other health problems.

**Selection of a Foreseeably ‘Vulnerable’ Population**

The children selected to participate in this project came from four social groups, with poor economic backgrounds – scheduled tribes, scheduled castes, Muslims and other backward classes. In both Gujarat and Andhra Pradesh, the majority of the participants were tribal children, whose parents were agricultural labourers. Some girls were from families that had been displaced by the conflict in the neighbouring state of Chhattisgarh; circumstances that only serve to compound their vulnerability.

**‘Captive’ participants**

The majority of the girls vaccinated in Bhadrachalam, were residents of *ashram paathshalas* (boarding schools). The selection of these girls for the project is striking, given that they live away from their parents, and hence cannot be monitored by them, nor can the parents...
respond to any adverse developments in their children’s health. This also allowed the trial providers to conveniently sidestep the provision of parental consent. A camp was set up in the hostels and school campuses to administer the vaccine.

Though the ICMR Ethical Guidelines for Biomedical Research on Human Participants require researchers to justify the involvement of those with ‘reduced autonomy as research participants, since their consent may be under duress or due to various other compelling reasons’, no such justification has been made public regarding the HPV vaccine research in Andhra Pradesh and Gujarat. Moreover, although the Investigative Committee’s report states that “there was no specific targeting of any particular group or class except that the plan called for including a predominantly urban, rural, and tribal block in each selected district”; it goes on to say that “...for better understanding of the research nature of the study and its impact on cancer prevention a higher strata/better educated/better aware population inclusion might have been more desirable. The tribal and more difficult areas could have been chosen in the later round. The standard of medical care in remote areas is generally not of the same level as in the urban areas. It would have been easier to provide proper medical care at an urban district level for an SAE, particularly a life threatening one. In addition to that, the entire event would have been better investigated to pinpoint the cause of the illness even if unrelated. The adequacy of existing AEFI (Adverse Events Following Immunisation) system to measure 4 out of 5 primary endpoints also could have been better tested in the urban area first”.

**Travesty of Informed Consent**

In many instances, the wardens/teachers of the residential schools and hostels were asked to provide consent or permission for vaccination, while parents were not informed that their children were taking part in a clinical trial. The ‘consent form’ was used primarily in the case of non-residential schools, and children were asked to get signatures from their parents. Girls were given HPV Immunisation Cards, which were in English - a language that neither the girls, nor their parents, were familiar with.

In Andhra Pradesh, an authorisation circular was issued by the Deputy Director, Tribal Welfare Department, Khammam, giving permission to the hostel wardens/head masters of residential schools to sign on the consent forms on behalf of the girls being administered the vaccine. Though both Schedule Y of the DCA (MOHFW 2005: 510) and the ICMR guidelines (ICMR 2006b: 28) require that trials on children can be undertaken only with the consent of the parent or guardian, and with the assent of the children where appropriate, the interviews suggest that neither was done. Further the Committee’s report states:

“…this authorisation runs contrary to the basic principles of obtaining consent as students cannot be considered to have full autonomy in front of their teachers/headmasters.
There is no express approval of the Institutional Ethics Committees (IECs) of MNJIO&RCC (MNJ Institute of Oncology & Regional Cancer Centre), Hyderabad for this provision, nor is there any mention of it in the consent document”.

Incorrect Information

Everybody involved in the project (the wardens, teachers and students) believed that the vaccine was part of the public immunisation programme, and had no idea that they were, in fact, part of a research study. They were not even aware that they had a choice regarding participation in the study. Many of them stated that they were given to understand that the government was providing free of cost, an expensive vaccine that would prevent ‘uterine’ or ‘cervical’ cancer. This would otherwise be unaffordable for them. Several parents brought their daughters to the vaccination camps themselves when they heard about the project. One mother said, “Since it was a vaccine being given by the government, we all trusted it blindly and considered it reliable, like any other vaccine that is given in the immunisation programme”.

Lack of Follow-up/Compensation/Insurance for the Participants

The fact-finding team discovered that post vaccination many of the vaccinated girls were suffering from stomach aches, headaches, giddiness and exhaustion. There were also reports of early onset of menstruation, heavy bleeding, severe menstrual cramps, extreme mood swings, irritability, uneasiness and restlessness, following the vaccination. No systematic follow up or monitoring was carried out, either by PATH or by the ICMR. The enquiry committee has identified seven deaths amongst the participants post vaccination (five in Andhra Pradesh and two in Gujarat), even though they claim that these deaths were not linked to the vaccine.

Their report states, “One of the major deficiencies of the study in retrospect was inadequacy of the preparedness for tackling Serious Adverse Events (SAEs) and deaths, whether related or unrelated to the vaccine. The deaths were noticed long after their occurrence, when the preparations were on for the next round of vaccination. And then no independent body of experts analysed the cause of deaths”. Further, deaths and AEs following vaccine administration were also not investigated by the District Immunisation Officer (DIO) or District RCH Officer (DRCHO).

The Drugs and Cosmetics Act clearly outlines that ECs are responsible for the review and approval of trial protocols so as to safeguard the rights and well being of trial subjects, especially those from vulnerable sections of the population. The EC in the HPV case appears to be reluctant to be held accountable for violations in the HPV trials.
The investigative committee has also stressed on, “the need for continued pharmacovigilance of the HPV vaccine” and reiterates the rule 122-E of the Drugs and Cosmetics Act, that “all vaccines, in particular the HPV vaccine, shall be treated as new drug for four years from the date of their approval in India. All research studies (including clinical trials) that involving administration of a new drug (vaccine), even after licensing, should proactively monitor and investigate all adverse events, more so the SAE and deaths irrespective of their appearing or not appearing to be related to the vaccine”. The committee report further mentions that every research must include an in-built mechanism for follow up, monitoring and compensation either through insurance or any other appropriate means, to cover all foreseeable and unforeseeable risks. The committee has also questioned why this provision was not followed, especially in lieu of the fact that PATH itself had an insurance cover for the projects.

**Role of the State and an Intentional Blurring of Distinction**

The committee, through its report, has highlighted the ‘blurring of the distinction between the National Immunisation Programme as a routine service activity, and the research nature of the HPV vaccination project’. The HPV immunisation card given to girls who were administered the vaccine in Bhadrachalam, carried the logos of the National Rural Health Mission (NRHM) and PATH. This raises questions about the role of the NRHM in this research, given that there is no mention of such ‘projects’ in its mandate.

Further the vaccine was administered either through the Auxiliary Nurse and Midwives (ANMs) at the local Primary Health Centres, or through a camp approach in the schools. In some cases in Gujarat, the Accredited Social Health Activist (ASHA) was sent to take consent from the parents, and in others the ANMs met with the parents to explain the ‘benefits’ of the vaccine. In Bhadrachalam, all involved (wardens, parents, teachers and students) believed the project to be part of the public immunisation programme, and had no idea that they were in fact, part of a research study. They were not even aware that they had a choice regarding participation in the study. Also, the existing health infrastructure in trial sites (particularly in Khammam district) is grossly inadequate. Pap smear facilities are conspicuous by their absence in all government facilities in the area. The vulnerability of these communities is thus further compounded by of lack of access to healthcare, information, and systems for reporting adverse events.

In the public sector, Pap smear facilities are limited to tertiary level facilities, where these are usually offered to women with symptoms of reproductive tract infections or
advanced cervical cancer. Above all, vaccination can never be considered as a substitute for screening. All women, including those who are vaccinated, need to continue with regular Pap test screening since the preventive effect of the vaccine on cervical cancer has not yet been proven.

**Absolute Lack of Transparency and Accountability**

Despite a clear case of violations, and foolproof evidence thereof by the experts appointed, the ‘Responsibility’ section of the report is the weakest. Moreover, the Committee exonerated everyone involved in the project. Even the glaring conflict of interests with the involvement of two pharmaceutical companies providing the vaccines free of cost, failed to illicit a response. The vaccines have been shrouded in secrecy from the initial Phase III trials conducted prior to licensing, right up to the disclosure of the Committee's findings. It has also been a struggle to get any information in the public domain, with all those involved being completely unresponsive.

**Presentation III - The Conduct of Unethical Trials at the Bhopal Memorial Hospital and Research Centre**

**Ms Rachna Dhirgra**

I work with the survivors of the Bhopal gas disaster – the worst industrial disaster, in which over half the city (500,000 people) of Bhopal was exposed to a poisonous gas. This resulted in over 23,000 deaths till 2010, due to gas exposure related illnesses. Over 150000 people in Bhopal continue to suffer from chronic illnesses. Before talking about the clinical trials conducted on this population, I would like to give some background about the Bhopal Memorial Hospital and Research Centre (BMHRC). This hospital was set up as per the order of the Supreme Court of India, as a part of the settlement, wherein, Union Carbide was asked to provide a 500 bed hospital to cater to the health needs of the gas victims. However, this super speciality hospital, functional from the year 2000, began with the biased mandate of providing services to private patients, along with free services for those affected by the gas disaster. Gradually, the private practice of the hospital has taken over the original objective of providing free services to those in real need.

From 2004 to 2008, the BMHRC was engaged in ten different drug trials involving pharmaceutical companies such as Pfizer, Wyeth, Astra Zeneca, GlaxoSmithKline, etc. Trials were conducted on 279 patients, of which 215 were ‘gas patients’. In response to an RTI inquiry, the hospital stated that 80 per cent of the trial participants were ‘free patients’, i.e. those entitled to free services at the hospital, in other words, gas victims.
While the hospital records show ten different trials, the response to the RTI application, however, mentioned only six. Moreover, there is evidence that the hospital has, in fact, received money to the tune of one crore rupees, for at least ten different trials. The American ‘clinicaltrials.gov’ site states that there were 13 registered clinical trials at the hospital. The variations in these numbers reflect the lack of systematic data regarding these clinical trials. Also, the actual information regarding the drug trials at the hospital came to light only in 2010, when a flier stating that all clinical trials must be stopped fell into the hands of the media. This flier was addressed by Justice Ahmadi to the Director of BMHRC and was dated 2008. Until then, there was no knowledge of these trials in the public domain.

The DCGI had information only on six trials, which included:

- There were 11 deaths, of which 10 were gas victims. None of these deaths were attributable to the drugs.
- In a trial for the drug Televancin for hospital induced pneumonia, four people were tested, three of whom died during the course of the trial.
- In another study for Fondaparinux, a blood thinner, 57 people were recruited, of which 55 were gas victims and six of them died.
- In the Tigecycline (a drug for abdominal infections) study, 30 people completed the study and two people died.
- In another study by Eli Lilly for a drug called Prasugrel, according to the information given out by the DCGI, the study was never initiated at BMHRC. However, we know from inside information that the study did take place and several people died due to haemorrhage caused by the drug.

BMHRC has an Institutional Review Board (IRB), which has 19 members, of which 13 were from within the hospital, including doctors who had themselves been PIs of different studies. The secretary of the IRB also happened to be the wife of one of the PIs; another member was operated free of cost by one of the PIs. Almost none of the deaths were reported to the IRB within 7 days of its occurrence, as demanded by the protocol. In most cases, they were reported only after the study was over.

The state of Madhya Pradesh decided to launch an investigation into these trials. The State Drug Controller, Dr Sahoo, was asked to bring out a report of the findings. This report is still pending.
Some salient points so far:

- No informed consent was taken from any of the participants. Doctors working at the hospital at the time, who were not happy with the way things were being done, have gone on record to state that they were forced to sign on the consent forms.
- So far, no compensation has been given to any of the participants, neither for death nor to reimburse the expenses of the participants. We have a copy of the contract that clearly states that compensation must be given for meals, travel, etc.
- The doctors were given up to Rs 9000 per patient recruited.

The fact that this hospital was built to cater to the health needs of the gas victims was well known. Moreover, everyone involved, including the pharmaceutical companies knew that the bulk of the patients were suffering from the after effects of the gas leak. These people with reduced autonomy were nevertheless enrolled for these trials against all protocols and ethical guidelines. We see a clear parallel between the Bhopal gas disaster, and the clinical drug trials that have been conducted at this hospital. The fact that Union Carbide in 1984, and the pharmaceutical companies now, have gotten away with no legal liability or punitive action is indeed appalling.

**Presentation IV - Unethical Clinical Trials at MGM Medical College**

**Dr Anand Rai**

Indore, the commercial capital of Madhya Pradesh (MP), is surrounded by backward and predominantly tribal districts. Poor patients from surrounding districts flock to Indore for secondary and tertiary healthcare. In fact, since 2005, Indore has transformed itself into a clinical trial hub, with increasing hospitals, as well as greater air travel connectivity.

As per an investigation carried out by the MP Government’s Economic Offences Wing, a total of 73 clinical trials were conducted on nearly 3300 patients at the Maharaja Yeshwant Rao (MY) Hospital, a teaching hospital under the Mahatma Gandhi Memorial Medical College (MGMMC). Of the 3300 patients, 1833 were children. The trials were carried out by six senior doctors who were paid Rs 5.1 crore by eight Indian drug companies and institutions. Sponsorship was also received from 22 multinational companies and institutions. Following the trials, 81 participants including 18 children, suffered serious adverse effects, which included death. At about the same time, nearly 60 trials involving 40 doctors (the number of patients was not disclosed), were conducted in the private sector. In the CHL Apollo Hospital, Indore there were five deaths.
I was working in the Ophthalmology Department and I received a number of patients, who had suddenly developed cataracts. On investigating, I realised that these patients were part of a clinical trial for a drug, of which cataract was a known side-effect. I realised that the trials were being conducted unethically in the hospital. I also discovered that these trials had been banned in the US by the USFDA, and were being illegally conducted at the MGM College. When I tried to complain, I received no cooperation and was threatened instead.

**Figure 26**

<table>
<thead>
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<th>Name of Drug/vaccine</th>
<th>Sponsor</th>
<th>Number of children involved</th>
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<td>Easy five vaccine</td>
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<tr>
<td>Men ACWYTT Conjugate vaccine</td>
<td>GlaxoSmithKline</td>
<td>194</td>
</tr>
<tr>
<td>DTWP Vaccine</td>
<td>Panacea Biotech</td>
<td>100</td>
</tr>
<tr>
<td>VALSARTAN</td>
<td>Novartis</td>
<td>05</td>
</tr>
<tr>
<td>Bivalent OPV vaccine</td>
<td>WHO</td>
<td>400</td>
</tr>
<tr>
<td>Pentavalent</td>
<td>L.G. Lifescience</td>
<td>160</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Johnson &amp; Johnson</td>
<td>03</td>
</tr>
<tr>
<td>Imovax Polio Vaccine v/s Panacea Biotech vaccine</td>
<td>Sanofi Pasteur</td>
<td>65</td>
</tr>
<tr>
<td>12AH1N1 Vaccine</td>
<td>Serum Institute of India</td>
<td>50</td>
</tr>
<tr>
<td>12BH1N1 Vaccine</td>
<td>Merck and Dome</td>
<td>44</td>
</tr>
<tr>
<td>HPV Multivalent vaccine V-503</td>
<td>Crucell</td>
<td>90</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalent oral polio vaccine</td>
<td>Panacea Biotech</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1838</strong></td>
</tr>
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</table>

Figure 26 gives a list of the various vaccine trials that were conducted. The trial for Polio Vaccine was conducted on a two day old child, which resulted in an allergic reaction. The child developed white spots all over his body. Four other children suffered from serious adverse effects. None of the families of these children were given any form of compensation, nor were these events reported to the EC. We got access to this information by raising questions in the State Assembly through a local Member of Legislative Assembly (MLA).
**Ethics Committee**

The EC at MGMMC has 27 members with no representation from non-medical members. Of the total, 22 are professors from within the college. The IECs at the Netaji Subhash Chandra Medical College and Bombay Hospital, Indore are chaired by a veterinary doctor. These committees are not independent; in most cases the chairperson is part of the institution, and in some cases, the EC is located in another town altogether.

Some recent findings by the Economic Offences Wing with regard to the ECs are as follows:

- Members of the EC at MGMMC were the PIs in many trials. The Secretary of the Committee, Dr Anil Bharani failed to follow the GCP and the ICMR guidelines.
- PIs failed to fulfill their responsibility in cases of serious AEs, and the basic tenets of informed consent were violated.
- Code of MCI Act 1958 (20A) in respect of Professional Conduct was violated.
- Patients enrolled for clinical trials stated that the process was not transparent.
- Insurance provisions for patients suffering serious AEs were violated. Consent was not taken as per the protocols.
- The stipulated income of ten per cent for trials has not been deposited with the institution.

This report is, however, not yet available in the public domain, and was obtained only through an RTI application. Following this report, several protests were held in Indore against unethical clinical trials, which prompted the State Government to appoint a committee headed by the Principal Secretary, Medical Education, to look into the irregularities. On 29 October 2010, this committee banned all new trials in the state. A public hearing was organised by the committee at MGMMC on 30 October 2010, wherein 168 persons made a deposition before the committee and gave their recommendations.

The Department of Public Health and Family Welfare of the Government of Madhya Pradesh, made the following suggestions to the DCGI on 22 March 2011:

1. A representative of the State Government should be included in granting permission and licences under Rule 21(B) of the Drugs and Cosmetics Act.
2. Any drug trial taking place within the state must have the clearance of the State Government before it is approved by the DCGI.
3. All serious AEs must be reported to the CMHO by the PI within 24 hours.

4. Director Health/Medical should have the right to audit and monitor the records pertaining to drug trials.

The issue has also been consistently raised in the State Assembly over the last four sessions and there has been much discussion in the house. Information related to about 20 issues that we were unable to get through RTI applications were raised in the Assembly by seven MLAs. Questions were also raised in the Rajya Sabha by Members of Parliament (MPs) such as Ms Brinda Karat.

Suggestions for Regulating Clinical Trials

- An empowered committee should work out the requirement for clinical trial based on the death toll and disease burden on the country. Only such trials where the numbers exceed a certain limit should be allowed in the country.

- The new drug proposed to be introduced in the country should be cost effective. All trials should be sponsored by/through the government.

- Placebo controlled trials should be stopped.

- Concurrent trials should not be allowed, and only those foreign drugs, which are already licensed in their home country, should undergo trials in India.

- There should be no restriction on publishing the results of a trial. In fact the publication of results in reputed scientific journals should be mandatory for the benefit of patients.

- An independent apex agency needs to be established to oversee the functioning of the DCGI office and various ECs.

- The office of the DCGI should be strengthened professionally to have more technical persons and inspectors. The DCGI should have regional centres so that trial sites can be monitored effectively. Help lines must be set up for complainants.

- All ECs should be registered with the GOI. In case they fail to carry out their duty properly, their registration should be cancelled.

- Failure to carry out their duty with respect of ethical clinical trials should result in punishment for the Principal Investigator, the drug company, chairman of the EC and the contract or clinical research organisation. The punishment should include fine and imprisonment.

- Funds for clinical trials should be channelled through institutions and not privately.
Each trial participant must be given a copy of the informed consent form, patient information sheet and clinical trial liability insurance policy for their protection.

If a drug is granted a licence after the trial, the trial subjects must be given a share of the profit.

Presentation V - HPV Vaccine Assessment Case Study and its Implication on Clinical Trial Policy with Regard to the HPV Vaccine

Dr Román Pérez Velasco

I would like to start by giving a background of my organisation Health Intervention and Technology Assessment Program (HITAP). HITAP is a non-profit making research organisation, which is associated with the Bureau of Health Policy and Strategy, of the Ministry of Public Health (MoPH). At HITAP, we assess a wide range of health interventions and technologies, including pharmaceuticals, medical devices, individual and community health promotions, and disease prevention.

Our main financial supporters include the Thai Health Promotion Foundation, the MoPH, Health Systems Research Institute, National Health Security Office, and other international agencies such as Global Development Network, the World Bank, and WHO. As a rule, HITAP does not accept support from the private industry, or from other for-profit organisations.

Vision:

- To appropriate health technologies for the Thai society.

Mission:

- To assess health technologies efficiently and transparently, using qualified methods (economic evaluation, qualitative and observational study, randomised control trials (RCTs), etc.
- To develop systems to promote appropriate management of health technology and health policy determination.
- To disseminate research findings with the view of informing and educating the public.

Scope of Work

Health technology: Application of organised knowledge and skills in the form of devices, medicines, vaccines, and procedures and systems to solve health problems and improve quality of lives.
Health Technology Assessment (HTA): Multidisciplinary field of policy analysis to study the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.

The Case of the HPV Vaccine

The important dates related to cervical cancer prevention policy in Thailand are:

<table>
<thead>
<tr>
<th>Year</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>Cervical cancer screening covered by public health plans in Thailand.</td>
</tr>
<tr>
<td>2006</td>
<td>Launch of the first HPV vaccine in the US.</td>
</tr>
</tbody>
</table>
| 2007     | • Two HPV vaccines licensed in Thailand  
           • A study to identify an optimal strategy for cervical cancer prevention in Thailand was conducted by IHPP and HITAP. Preliminary results were disseminated in December. |
| April 2008 | HITAP conducted a study on effect of disease awareness communication of HPV vaccine through mass media. |
| February 2008 | Research for development of an optimal policy strategy for prevention and control of cervical cancer in Thailand was launched. |
| 2008-2011 | Results were continually presented to both decision makers, e.g. MoPH and NHSO, and academic for a, e.g. UNFPA-WHO Asia Pacific Consultation. |
| September 2008 | HPV vaccine was not included in the Universal Coverage scheme. |
| Aug-Dec 2008 | MoPH introduced a campaign to boost screening coverage called ‘116-days initiative’. |
| December 2008 | HITAP conducted a study on the role of HTA evidence in decision making for HPV vaccination. |
| Feb-Apr 2009 | Prices of HPV vaccine reduced by half by pharmaceutical companies. |
| June 2009   | Together with the DoH, HITAP conducted a research on cervical cancer screening with VIA + Pap smear. |
| 2010       | The study found that screening coverage expanded from 20% in 2008 to 70% in 2010. |
| April 2011 | Health professionals requested MoPH to consider including HPV vaccine in the UC. |
| April 2011 | HITAP presented its studies in the MoPH meeting. |
| May 2011   | MoPH policy makers did not include the HPV vaccine in the national programme. |
| At present | Price negotiation continues... |

The important events in this timeline are:
- the approval of the vaccine in the private markets in 2007.
- the rejection of the HPV vaccines in the Thai public health sector in 2008.
- the scale up of screening services from 20 per cent to 70 per cent in 2009.
HITAP conducted four important studies during this period. The aim of the studies was to assess whether the HPV vaccine delivered ‘value for money’ as compared to traditional cervical cancer screening options (Visual Inspection with Acetic Acid, Pap smear). These studies used methods such as cost-utility analysis based on model-based economic evaluation, compiling societal perspectives in the Thai setting.

The results of these studies revealed:

- All screening options are cost-saving.
- VIA every five years (ages 30-45), in addition to sequential Pap smears every five years (ages 50-60) is the most cost-effective option.
- HPV vaccine becomes cost-effective if total vaccine price
  - < $270 (life-time duration of protection)
  - < $167 (10-year protection)
- The vaccine is less cost-effective if the screening coverage is higher.

Simultaneously, we also launched a qualitative cross-sectional study on the effect of mass media on Thai women, in terms of their perception, knowledge, and attitude towards vaccination. It was found that the information provided to Thai women was incomplete and inaccurate. This led many women to believe that this information came from the MoPH, for the welfare of the public, when it was clearly for commercial benefit only.

On the basis of the results of these studies, and the fact that it was unaffordable at the time, the MoPH rejected the introduction of these vaccines in the public health programme. While the entire Expanded Programme on Immunisation that included 12 childhood vaccines cost the State $29 million per annum, the HPV vaccine alone cost the government $80 million per annum.

Some of the other factors that led the Government to reject the vaccine included:

- Scaling up of screening programmes in 2008 – MoPH scaled up screening to cover one million women within 116 days.
- Political will of Government - A senior advisor in MoPH stated, “I informed the Minister that if he pursued this policy, he would win the hearts of all women. Then, he agreed and gave me the green light.” Another senior official stated, “If the minister pushed it, it could be successful and he would gain social credit without any significant additional investment.”
Influential factors – High burden of disease, political instability, and dissemination of evidence, which pointed out that the vaccine was cost-ineffective.

Therefore, in the past 5 years, we found that:

- 68 per cent women undertook cervical cancer screening at least once.
- 88 per cent of those did a Pap smear, while only seven per cent did VIA.
- Cervical cancer screening was done at health centres (50 per cent), public hospitals (30 per cent), private hospitals /clinics (15 per cent), and mobile units (5 per cent).
- The undertaking rate for cervical cancer in the past five years has gradually increased from two per cent in 2005 to 13 per cent in 2008. In 2009 there was a scaling up of cervical cancer screening, which jumped to 39 per cent.
- This pattern is similar to the cumulative rates that went up from four per cent to 68 per cent during 2005-09.

Thus, to conclude, the findings of the assessment done by HITAP may be detailed as below:

- Reduced pressure from the public; study provided policy options (VIA+Pap smear)
- MoPH introduced a campaign to extend coverage of cervical cancer screening, This was called the ‘116-Day initiative’.
- Current cervical cancer screening coverage of 70 per cent.
- This increase in screening could avert 1500 new cervical cancer cases, and 750 female deaths per annum. Also it saved the Government $ 6 million per annum in terms of treatment of advanced cancer cases.
- In February and April 2009, drug companies announced a significant price reduction. In May 11, a further price reduction was offered.

Comments from the Discussants and Chair

Ms T.K. Rajalakshmi

- The Thai experience with the HPV vaccine can be treated as a lesson as far as vaccine policies are concerned. Considerable amount of time and effort were spent to analyse the implications (social, ethical and economic) of each option, before arriving at a conclusion regarding the introduction of the vaccine into the health system.
• The presentations indicate that the poor, especially from vulnerable communities, unorganised sectors, and slum colonies, continue to be targeted, and there is no system of punitive action in this context.

• The approach of the Indian State, with an increased use of the Public Private Partnership (PPP) model, is intrinsically based on the exploitation of the poor.

• The HPV vaccine campaign has highlighted the importance of raising the issues of violations at different levels in the public domain to demand accountability.

• Another issue of concern is the blatant use of government functionaries such as the ANMs and ASHAs.

Dr Mohan Rao

• It is important to understand whether these are wicked people doing these things, or these are stray incidents, or they are, in fact, intrinsic to the way the global pharmaceutical companies are organised.

• The other thing that needs to be considered is the rubric of technologies. There is an over determined approach to public health that systematically ignores the social determines of health and instead supports what Kaushik Sunder Rajan describes as the ‘pharmaceuticalisation’ of health.

• At the heart of the 12th Five Year Plan document, there is an increasing role for health financing by the State, and the provisioning of health by the private and NGO sector. What we see is a serious threat to the State’s role. Thus, leading to the systematic emptying of the State, a very serious and dangerous issue at hand leading to the culture of impunity that we have in the health system as a whole.

• There is an urgent call for the assessment of all the technologies available in the public health system in the very manner that Thailand has done.

Dr Anant Phadke

• There is an urgent need to stress on the accountability of the State, and focus on bringing cases of violation to justice.

• There is also a need to push for banning of financial and material incentives to participants of trials, in order to minimise misuse, and to ensure that the only incentive for people to participate in the trials is the benefit of a new drug.

• There is an uneven balance of powers between the pharmaceutical companies and the trial participants worldwide, wherein the participants are invariably rendered vulnerable along with the uncertainty of a clinical trial. In such a case, we must insist
on a clause that bans the recruitment of ‘poor’ participants from tribal communities, or those below the poverty line, as a moratorium, which must continue until regulatory mechanisms are strengthened in an enabling environment.

- It is important to carry out a cost-benefit analysis before introducing vaccines into the Indian public health system.

- There is an urgent need for further discussion on the issue of deaths and their compensation and management during the course of clinical trials. We must closely analyse the short-comings in the process of clinical trials during which horrendous violations take place.

- We cannot make blanket statements regarding the banning of placebo controlled trials, and should instead analyse and discuss these issues further.

- Public funding of clinical trials requires further discussions, as the duty of the corporate sector towards contributing to research should not be taken away completely. Instead one can argue for public control of research.

Discussion Points

- Participation in clinical trials has become a form of an alternative livelihood of sorts. Therefore, no money should be give to participants; this will reduce the over enthusiasm of the participants.

- Why is it that in the face of widespread unethical practices, there is such little public outcry? If the pathology is so widespread, why are there no whistle blowers? This is a very important aspect in today’s context as over 22 RTI activists have been killed recently.

- We must make the government accountable. The lobbies are extremely strong at every level. There is enough information to show that the government is not willing to take any action; all we need to do is to plan the way forward.
All sessions during the two-day consultation were aimed at developing concrete recommendations for policy as part of their presentations. Time was allocated in each session during which the floor was open to questions and comments, debate and discussion and also towards consensus building around concrete policy recommendations. A brief was prepared by a core group that streamlined the salient points that had emerged from the discussions of the previous sessions. The purpose of a brief emerging out of the recommendations, would be disseminated to and discussed with representatives from the MoHFW, including the ICMR and the DCGI, and other policy makers; the brief was to be released to the national and regional media towards creating public opinion and awareness among various constituencies.

In this particular session, *Moving Towards People Centric Clinical Research*, the chairs presented the brief for further discussion, debate and consensus. Each point was discussed in detail. While no consensus was reached on some issues, there was agreement on several others and the following press brief was finalised. The debates were located in a larger critique of liberalisation and the failure of the government to secure ethical norms and unregulated proliferation of trials. Questions and concerns regarding the framework of ECs and their constitution were raised towards avoiding a conflict of interest. Further, details of the range of alternatives were discussed with a debate over how much burden the state can shoulder and if institutional committees, in principle, should be discarded. There was agreement over the fact that the present structure of ECs was not working and needed to be foregrounded. That medical research should be seen as part of healthcare practice and thus be built into the ethics of medical practice, was articulated. It was also reiterated that regardless of the extent of regulation, without ethics it would not work; constant supervision and monitoring may not be always possible. The nature of research in drug trials and the role of CROs was debated; questioning their status as research organisations and whether we can ask for abolishing CROs.
Some issues and suggestions on which no consensus could be established and needed further evaluation and discussion were those of biometric identification of participants, on grounds of practicality, and the conduct of clinical trials only in the public health institutions.

There was a suggestion to demand for a moratorium on recruitment of poor people and tribal people in clinical trials as the track record of pharmaceutical companies with regards safety of patients, citizens, especially in countries like India has been quite dubious. The supportive health infrastructure in rural, tribal areas to deal with medical emergencies is also grossly inadequate. Although, some of the participants agreed, others were not in favour of a moratorium.

A broad ambit of demands was agreed upon, such as anything unethical should become illegal; regarding law, it was essential to give teeth to the current policies of regulation; protection of whistle-blowers; action over past violations such as in HPV trials. Suggestions for research focussing on participants were discussed, in order to build a more informed perspective. Taking away incentives for investigators and regulators was emphasised by all. Better public funding and support for healthcare services and training of personnel and EC members was largely agreed upon. Consensus was established over post-trial benefits and comprehensive health insurance. While travel reimbursements may be permitted, further discussion needs to take place over what is considered a reasonable amount for the same.

The need for greater collective discussion after such a consultation was felt by all in order to move towards structural alteration and articulation of more concrete demands.

Call for Regulation of Drug Trials in India

A press brief from the participants of the National Consultation on Regulation of Drug Trials in India

Participants at the National Consultation on Regulation of Drug Trials, organised by Sama, Low Cost Standard Therapeutics (LOCOST), Centre for Studies in Ethics and Rights (CSER), All India People’s Science Network (AIPSN) and Drug Action Forum-Karnataka (DAF-K), in New Delhi during 26-27 September 2011, expressed their deep concern regarding the unregulated proliferation of ill-regulated clinical trials in India following the liberalisation of norms for the conduct of such trials in 2005.
The government has aggressively encouraged foreign drug trials in India without putting in place structures to protect its participants. Regulatory mechanisms have proved to be grossly inadequate and ineffective. The Central Drugs Standard Control Organisation (CDSCO), which is the principal regulatory agency, lacks both in capacity and in the will to carry out its functions that include the scientific review of trial protocols and monitoring the conduct of trials. Ethics committees are ill-equipped, untrained, and not accountable for their decisions.

There is no evidence that the liberalisation of norms is contributing to an improvement in access to essential medicines in India, or to the enhancement of the country's scientific and research capacity. On the other hand, there is mounting evidence of human rights violations and occurrences of adverse events to the participants in these trials.

Physicians receive incentives to recruit patients for the trials, and they sometimes do so without obtaining their informed consent. Participants are also subjected to unethical practices such as deprivation of effective medicines. Medical treatment and compensation are denied for the growing number of trial-related injuries and deaths. Bioequivalence trials offer participants large payments as compensation, in blatant violation of existing ethical guidelines. This induces poor people to risk their lives in these trials.

Reports from Ahmedabad, Bhopal, Indore and Bhadrachalam (Andhra Pradesh) provided an indication of the type and scale of unethical and outright illegal trials conducted on the poor and marginalised groups in India. Such practices are situated in the overall context of an unethical medical practice in a system where healthcare is either inaccessible or unaffordable.

Clearly, liberalisation of norms for the conduct of clinical trials in India has belied its promise and instead introduced fresh challenges in the health care sector of the country.

The Consultation also made the following specific recommendations:

**Update Laws and Guidelines on Clinical Trials**

1. The 2005 amendments to Schedule Y of the Drugs and Cosmetics Act, liberalising the conduct of clinical trials in India need to be reversed, and the loopholes that result in deficiencies in regulation need to be addressed. Non-compliance with the provisions in the Drugs and Cosmetics Act needs to be made justifiable and punishable.

2. The Bill on Biomedical Research on Human Participants, incorporating the ICMR's Ethical Guidelines for Research on Human Participants, must be codified into a law.
3. The ethical guidelines enlisted by the ICMR must be revised to remove inconsistencies and loopholes, and also updated to take into account developments since 2006.

**Regulate Sponsors, Trial Organisations and Investigators**

1. Pharmaceutical companies, who are the major sponsors of clinical trials, work through Contract Research Organisations (CROs) and a network of individual researchers in government and private medical colleges as well as in large and small hospitals. Regulation is necessary at all levels of this network.

2. Recruitment incentives to investigators should be banned. Compensation to participants must not be so large that it serves as an incentive.

3. Complaints of unethical research must be investigated immediately and punitive action taken where necessary. The reports of unethical and illegal drug trials in Bhopal, Indore, Ahmedabad and Bhadrachalam as well as elsewhere must be investigated, the findings made public and the perpetrators punished.

4. Whistle blowers must be provided protection.

**Ensure Reporting, Treatment and Compensation in Case of Injury or Deaths in Trials**

1. The CDSCO must ensure that CROs send prompt notification for all injuries or deaths in a trial, followed by the investigation findings and the action taken on these findings, including the compensation paid.

2. Companies should be required to provide comprehensive health insurance for all trial participants to take care of all health needs (including ancillary care).

3. In case of study related injury, disability, or death in human participants, the law should hold the sponsor accountable and liable.

**Strengthen Regulating Institutions**

1. The CDSCO must be assured sufficient resources and trained manpower to conduct technical review of applications, and monitor the conduct of trials including surveillance and safety studies.

2. ECs must be registered, accredited, made accountable and liable for their decisions. EC members must be trained, and should have the capacity, resources and the independence to review and monitor drug trials.

3. The current system of ethics review needs to be revised to address the important issue of conflict of interests amongst the EC members and other aspects of clinical trials.
Restrict Research on Vulnerable Populations

Research on vulnerable populations must have a strong justification, (such as a condition found primarily among that section of the population) and an assurance that these participants will reap health benefits from participation. This assurance should not be viewed as an incentive to enter the trial.

Ensure Post-Trial Access

All drugs developed through trials in India must be made available to the trial population free of cost for as long as they are available in the country, after which time they must be available to everyone at an affordable price.

Ensure Transparency

1. Trial-related information of public relevance should be available in the public domain.
2. Confidentiality clauses in agreements between trial sponsors and regulators, and sponsors and investigators, need to be modified so that they do not block bona fide access to information on clinical trials which has a bearing on the health of trial participants.

Support Public Research

Industry-funded drug trials do not constitute research. We need to develop a strong research base starting from basic research to development and testing of drugs and other technologies relevant for public health and healthcare in India. Public funding is necessary for research to be driven by our health needs rather than companies’ profits.
The valedictory address was delivered by Dr P.M. Bhargava and the session concluded with remarks by the chair.

Valedictory Address

Dr P.M. Bhargava

The subject is extremely complex. I will confine myself to certain aspects of drug trials and share my views, on what I feel are the four most important aspects in this regard. To start with, I would like to talk about the history of diseases and health care in India, for in order to plan the future, it is important not only to understand the present but also the past. Then I will share with you the current scenario in India and elsewhere, followed by the negative aspects of this scenario, and finally what I believe should and can be done to improve the current situation.

One of the major burdens that mankind has borne right through history, besides finding food and shelter, is disease. Some diseases are new, like Acquired Immuno Deficiency Syndrome (AIDS) and Severe Acute Respiratory Syndrome (SARS), but most diseases that we know today appear to have been in existence throughout human history. However the burden of diseases has probably been much lower than it is today and one of the reasons for this is the manifold increase in lifespan. Therefore, finding ways and means of combating diseases is one of the major challenges face by mankind. Several approaches have been used in the past and continue to be used even today, to tackle medical and health problems. These include surgeries, dietary control, change of environment, treatments such as yoga, physiotherapy, etc. and drugs.

In the beginning, the drugs were entirely plant based; this was later followed by synthetic drugs. The plant based drugs were made by traditional doctors on the basis of the five systems of medicine, but as business became more and more organised, drug companies were set up and the invalid traditional formulations started getting marketed. Attempts were then made to discover active ingredients in these plant based products. In the first quarter of the twentieth century, man’s knowledge made great advances particularly
in two areas – organic synthesis, and the structure of functional relationships in the chemical world. The knowledge of organic synthesis led to the manufacture of synthetic compounds; these were the same compounds, which until now had been obtained from natural sources. The understanding of the structural and functional relationships in drug action led to the discovery of new drugs, and drug companies started looking for ‘new chemical entities’.

As lifespan increased, there was a need to discover newer and better drugs for age related problems such as Diabetes, Dementia, Alzheimer’s disease, Parkinson’s disease, etc. In addition to this, the eradication of Small Pox emphasised the need for prevention of disease through vaccines. The demand for newer and better drugs was growing exponentially, providing impetus to the drug industry. There were large investments and returns at stake; this brought up the importance of regulation, and the regulatory regime became even more stringent. Until the first quarter of the twentieth century, the primary motive was altruistic and the main aim was to provide better and more effective medical and health care. But slowly, this motive changed towards making more money.

**The Current Scenario**

Today, to discover one new chemical entity, a drug company begins with thousands of synthetic compounds. For all these compounds, the company incurs the costs of synthesis, preclinical studies, checking the activities of the compounds in vitro systems, checking the toxicity through different phases of trials, etc., and finally only one entity gets to the markets. This entire process is governed by protocols that take into account the history, the requirement, the material, and the background of the drug. In addition to this, the inclusion and exclusion criteria for the trials, the time frame, the dosage, and the parameters to ascertain the success of a drug must also be closely examined. Lastly, a consent form in various languages, institutional ECs, provisions for compensation, etc. must be drawn up.

CROs have also been set up specifically to identify investigators, to keep checks, and ensure that protocol is followed. They are also responsible for collecting samples and transporting them to the analysis site. It is however important to recognise the limited roles of the CROs, since they have nothing to do with research; it is like contracting out a job. Despite this elaborate setup, today the number of new chemical entities that get into the market has gone down, dramatically. Fifteen years ago, sixty new compounds came into the market each year. Last year the number was down to only ten. This demonstrates the tremendous pressure on the drug companies.
Today, if a drug does not fetch a minimum return of one billion dollars in return per year, drug companies do not work on that drug. It costs about 1.5 billion dollars to discover a new drug and it takes 15 years from the initial discovery of the drug until the point where it can actually be launched in the market. Rational drug design, based on an increased understanding of drug action has reduced this time period to ten years and the cost to a little less than a billion dollars. However, the demand for new drugs has increased parallel to the increase in the burden of disease, because of lifestyle. For instance, we need newer antibiotics due to increased resistance of drugs, but the supply on the other hand has decreased. Therefore the temptation to cut corners in the entire process has increased.

**Issues and Problems**

- Incomplete and inappropriate dossiers, which do not give complete information. Sometimes, the idea itself is flawed. For instance, in the case of the HIV vaccine, we have to consider whether it is really appropriate to conduct a trial for such a vaccine.

- There is a political influence involved in the business of influencing the approval authority, DCGI, GOI, MoHFW, etc.

- Support is given only to those scientists who give desired results. A meta-analysis was conducted in this regard, which found that most scientists manipulate results to give the drug companies the results they seek. That is why today, many prestigious journals ask scientists to state the source of funding, in order to ascertain whether there is a possible conflict of interest.

- All results are not reported by the drug companies. SAEs are often not reported in the final results.

- Informed consent is not taken; touts lure the participants with incorrect information. Legitimate interests of the trial participants are not accounted for. There is political influence on this. Drug companies also exercise political influence.

- There are a large number of unregistered, unrecognised CROs, Hyderabad has around 50 CROs and not all are registered. They often overstep their terms of reference and do not discharge their duties appropriately.

- Corruption is another major problem.

- Healthcare is becoming increasingly commercial and the government is abdicating its responsibilities.

- Adverse fallout of liberalisation – not even using the favourable provisions of the TRIPS agreement. Article 27.1 in TRIPS makes it mandatory for product patents, but 27.3, 7 and 8 provide for exceptions to patent in public interest. The point being made is that the government could have interpreted these clauses in a way that would
have provided more safeguards, by providing more detailed exceptions to patenting. However, the government did not do so because its ideological commitment to neoliberal policies, that see patents as a positive factor.

- There are a large number of players in the field of drug discovery and drug trials (scientists, drug approval authorities, IECs, CROs, investigators), but there are no appropriate regulatory systems.

It is important to recognise that drug trials are important for new drugs to be assessed and validated. We do not want to stop the trials. However there is an urgent need for stringent ethical standards to protect the rights of all those participating in the trials, right from the investigator to the research participant. We should strive towards a system or a protocol that eventually supports the truth.

**Future Strategies**

We must recognise why India has become a clinical trial destination – large number of treatment naive patients, lower costs of trials; high levels of expertise, presence of large number of CROs, corruption, no language problem, and above all the largest biodiversity compared to anywhere else in the world. We should also recognise the fact that the problems of clinical trials are partly related to the overall ethical, intellectual and financial corruption that we face in the medical profession, right from education to practice.

We need to set up a clinical trial regulatory body. This body must have a representation from the civil society consisting of knowledgeable and upright people. The possible terms of reference for such a body are as follows:

- To bring about appropriate changes in legislation.
- To ask the fundamental question – is the trial really required?
- Redefine DCGI's responsibilities and have a mechanism to ensure that these responsibilities are actually discharged.
- Define the functions of CROs, and rechristen them as Clinical Trial Organisations (CTOs).
- Set up a system of accreditation and supervision of these CTOs.
- Accredit institutions and doctors who can partake in clinical trials; clearly state their responsibilities as well as how the institution or doctor will be compensated.
- Decide the number of trials an investigator can undertake at one time.
- Make sure that the agreement between the drug company and the institution takes care of the legitimate rights of the investigator. For instance the name of the investigator must be mentioned in publications.
• Accord a legal status to Institution Ethics Committees; decide on their composition and their supervision, define their terms of reference.

• Ensure that investigators fulfil their responsibilities in a fair and honest manner.

• Have a state ethics committee (in addition to Institutional Ethics Committee) to account for organisations that are not large enough to have their own IECs.

• Decide on compensation, travel money, loss of salary, insurance, etc. and ensure that they form part of the consent form.

• Have an in-built system of appeal, and state and define penalties.

• Work out a procedure of fast track approval of drugs that are intended for India-specific diseases.

• Formulate a mechanism for post-market surveillance.

• Set up transparent systems; for instance information on all approved trials, their protocols, DCGI’s decisions, IRB approvals, and SAEs, etc., should be available in the public domain. Transparency in drug trials is extremely important. This will help minimise corruption.

Each investigator must have a list of all other investigators in the case of a multicentric trial. In case of AEs, one investigator can then report to the other investigators. A system should be devised to strengthen the position of the NGOs interested in issues of medicine and healthcare and establish links with these organisations so that there is public participation in decision making. This has been done for other areas in the past, and can also be done for drug trials.

Once these basic terms of reference are agreed upon, specific terms can be made for vaccine and traditional plant based formulations. This is workable if there is a will; all it needs is a single legislation in its favour.

**Overall Comments by the Chair**

*Ms Brinda Karat*

Some of the basic demands that have emerged over the past two days of deliberation include:

• The new law, albeit delayed by 16 years, is on the verge of being passed owing to immense public pressure, and because it cannot be ignored any more. We can only hope that the draft will be open to expert comments and public consultations.
Those of us, who have been involved in these issues, have to make sure our voices are heard.

- The second point that has become very clear from the deliberations of the past two days is that of the complete failure of the existing regulatory framework of clinical trials in India. There is a need to re-emphasise the importance of State responsibility and accountability. Also, the State needs to have a direct role in the funding and the regulation of the industry, as well as the protection of the trial participants by making sure that the pharmaceutical companies fulfil their responsibilities.

- There is no point in tinkering with the structure of the ECs by adding new roles and responsibilities to their profiles; the framework itself is hollow and can never work within the existing structures. Therefore, we have to go beyond simply strengthening these committees. We have to question their current framework while at the same time strengthen the role of the ICMR and emphasise the importance of responsibility and accountability. Over the past few years, there has been a gross dereliction on the part of the ICMR in this respect and a dilution of its role. The HPV vaccine project, is just one example of this.

- The role of the State and its accountability cannot be emphasised enough. An immediate demand that should arise from this role is action from the Government on at least three cases of blatant violations – the HPV vaccine trials, the clinical trials at the MY Hospital, Indore and at the Bhopal Memorial Hospital and Research Centre.

- The debates and deliberations held here should also inform future strategies. For instance, some of the issues that need further discussion and effort include - discussion on the fundamental issue of what kind of trials should be carried out in India; documentation of cases of violations, information sharing and creating strong support to take up cases of rights violations; placing them in the public domain and making examples out of them.
GLOSSARY

1. Adverse Events (AE)
2. Adverse Drug Reactions (ADR)
3. Assisted Reproductive Technologies (ARTs)
4. All India People’s Science Network (AIPSN)
5. Clinical Research Coordinators (CRCs)
6. Central Drugs Standards and Control Organisation (CDSCO)
7. Competition Commission of India (CCI)
8. Contract Research Organisations (CROs)
9. Centre for Studies in Ethics and Rights (CSER)
10. Division of Scientific Investigators (DSI)
11. Drugs and Cosmetics Act (DCA)
12. Drug Controller General of India (DCGI)
13. Drug Action Forum, Karnataka (DAF-K)
14. Ethics Committee (EC)
15. Earnings Per Share (EPS)
16. Fixed Dose Combination (FDC)
17. Good Clinical Practice (GCP)
18. Human Papilloma Virus (HPV)
19. Indian Council of Medical Research (ICMR)
20. Intellectual Property (IP)
21. Institutional Review Board (IRB)
22. Informed Consent Format (ICF)
23. International Committee of Medical Journal Editors (ICMJE)
24. Indian Journal of Medical Ethics (IJME)
25. Institutional Ethics Committee (IEC)
26. Low Cost Standard Therapeutics (LOCOST)
27. Principal Investigator (PI)
28. Measurement System Analysis (MSA)
29. Mergers and Acquisitions (M&A)
30. Ministry of Health and Family Welfare (MoHFW)
31. Monthly Index of Medical Specialities (MIMS)
32. National Institute of Health (NIH)
33. National Medical Journal of India (NMJII)
34. National University of Juridical Sciences (NUJS)
35. Pre Conception and Pre Natal Diagnostic Techniques Act (PC & PNDT Act)
36. Request for Proposal (RFP)
37. Research and Development (R&D)
38. Right To Information (RTI)
39. Research Ethics Committee (REC)
40. Site Management Organisation (SMO)
41. Site Management Officer (SMO)
42. Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
43. Serious Adverse Event (SAE)
44. Standard Operating Procedures (SOP)
45. Trade Related Aspects of Intellectual Property Rights (TRIPS)
46. World Health Organisation (WHO)
47. World Trade Organisation (WTO)
Dr Amar Jesani

Dr Jesani is one of the founders of the Forum for Medical Ethics Society and its journal, *Indian Journal of Medical Ethics* (IJME), and is presently on its editorial board. He was National Coordinator of the two (2005 and 2007) IJME National Bioethics Conferences. He is also a Trustee of Anusandhan Trust, which runs the organisations, CEHAT (www.cehat.org) and CSER (www.cser.in) in Mumbai and SATHI (www.sathicehat.org) in Pune. He was on the national faculty of the ICMR for the NIH supported research bioethics training programme and is currently a visiting faculty teaching bioethics at five institutions in India.

Dr Amit Sen Gupta

Dr Amit Sen Gupta is associated with the Delhi Science Forum, a public interest organisation, working on science and technology policy issues. He is trained in medicine, and works on issues related to public health, pharmaceutical policy, Intellectual Property Rights and other science and technology issues. He is also part of the All India People’s Science Network (AIPSN) and is a member of the international secretariat of the World Social Forum. Most recently, he has edited the 3rd Volume of the Global Health Watch and is also currently the Joint Convener of the Jan Swasthya Abhiyan.

Dr Anand Rai

Dr Anand Rai was a faculty member in the Regional Training Centre, Department of Health and Family Welfare, MP Government, Indore, where he was also the President of the Junior Doctors’ Association. He has been actively involved in raising questions around the unethical conduct of clinical trials at the MGM college, through the use of RTIs and other legal tools. He is also the president of the Resident Doctors’ Association.

Dr Anant Phadke

Dr Anant Phadke is a leading member, from the late seventies, of a number of organisations - the Medico Friend Circle, All India Drug Action Network, LOCOST, Jan Swasthya Abhiyan - in the Health and Science Movements in India. He is Founder Coordinator
and now a Senior Advisor of SATHI-CEHAT, a leading NGO in the People’s Health Movement in India. He has authored over 250 articles in English and Marathi, books on the People’s Health Movement, and on varied issues and training manuals for Community Health Workers.

**Ms Anjali Shenoi**

Anjali Shenoi is a Masters graduate in International Development from the University of Bath, UK, and is currently working with Sama. She has been actively involved in the organisation’s advocacy initiative around a range of issues including Unethical Clinical Trials, Assisted Reproductive Technologies, Women’s Health and Rights, etc. She was also part of the fact-finding visit to Bhadrachalam, one of the trial sites for the HPV vaccine trials in India. She has also been a part of Sama’s action research projects including the most recent one on ARTs in India.

**Dr Arun Bhatt**

Dr Bhatt is the President at Clininvent Research Private Limited. He has an MD (Medicine) from Mumbai. He is a member of Faculty of Pharmaceutical Medicine of Royal College of Physicians UK and a Fellow at Institute of Clinical Research (UK). He has over 30 years of experience in the pharmaceutical industry. He has been a consultant in Pharmaceutical Medicine & Clinical Pharmacology and the President of the Indian Society for Clinical Research. He is Ex-Medical Director of Novartis India Limited and Ex-CEO of CMI (India) Pvt Ltd, a German Herbal R & D company. He is editor-in-Chief of Perspectives in Clinical Research and runs a regular column on Good Clinical Practice – Question Answers. He has over 100 publications in national and international journals and has authored a book Clinical Trials and Good Clinical Practice in India – Your Questions Answered.

**Dr P.M. Bhargava**

Dr Bhargava is one of the most distinguished and respected citizens of the country, known world-wide as a scientist, writer, thinker, institution builder, adviser to industries, and consultant. He conceived and built, amongst several major institutions, the Centre for Cellular and Molecular Biology (CCMB) at Hyderabad. He was the Vice-Chairman, National Knowledge Commission, Hyderabad. His scientific contributions include the preparation and characterisation of primary liver cell suspensions, identification of proteins from the seminal plasma and extensive characterisation of one of these proteins seminal plasmin. Amongst the over 100 major national and international honours he has received are - Padma Bhushan, Legion d’Honneur, the Wattumul Memorial Prize and
Goyal Prize. Dr Bhargava was a member of the National Security Advisory Board till November 2008. He is widely regarded not only as the architect of modern biology and biotechnology in India but also as one whose notable contributions have covered a wide range of human endeavours; from history to social analysis and the relationship between science and art.

**Ms Brinda Karat**

Ms Brinda Karat has been an integral and active member of the workers’ and women’s movements for over the last three decades. She has been closely associated with All India Democratic Women’s Association (AIDWA) and was also the first woman member of the Communist Party of India (Marxist) CPI(M) Politburo. She was elected to the Rajya Sabha as a member of CPI(M), on 11 April 2005 for West Bengal. During her tenure, as part of the Department related Standing Committee on Health and Family Welfare, Ms Karat has been instrumental in raising pertinent questions related to drug licensing, development and pricing and also on clinical trials; one such example is her involvement in highlighting the violations in the unethical conduct of the HPV Vaccine ‘demonstration’ project. Some of the other issues raised by Ms Karat include women’s political representation, campaign against hazardous contraceptives, violence against women, forest rights, coercive population policies, etc.

**Ms Deapica Ravindran**

Deapica Ravindran is the Junior Programme Officer at Centre for Studies in Ethics and Rights, Mumbai. She has a Masters degree in Biotechnology and is interested in the ethical and social implications of Biotechnology. She has been involved in maintaining a database on the clinical trials registered in the Indian registry CTR-I and the publication of *Clinical Trials Watch* in the Indian Journal Of Medical Ethics. Her current projects at CSER are *Biomedical and Health Experimentation in South Asia: Critical perspectives on collaboration, governance and competition*.

**Mr L. C. Goyal**

Mr L.C. Goyal is the Additional Secretary and Director General (CGHS) in the Department of Health and Family Welfare, Government of India, since September 2010. His duties include formulation and execution of key policy initiatives related to drugs control including IPR regime and food safety and standards, quality assurance, treatment protocols and standards, electronic based medical records (EMR), health insurance, registration and regulation of clinical establishments, procurement of vaccines and drugs,
vaccine security, matters relating to HLL and HSCC, human organ transplant, financing of public health through public private partnership, medical tourism and matters relating to Central Government Health Scheme (CGHS).

**Dr C.M. Gulhati**

Dr Gulhati has been Editor, *Monthly Index of Medical Specialties (MIMS)*, India, since 1980. His major interests over the years have been, and continue to be, clinical trials, marketing of medicines in India, drug pricing, medical ethics and drug laws in India. Among his many recent formal public commitments have been those of Member of the Advisory Expert Panel set up by the MoHFW on dealing with the H1N1 pandemic as it affected India; and Member of the Working Group on Spurious and Sub-standard Drugs set up by the Principal Scientific Adviser to the Prime Minister. He is also the drug expert on the popular Doctor NDTV website and related TV programmes. He contributes an article on drugs in every issue of the popular women magazine *Prevention*. Over the years, Dr Gulhati has spoken and written on a range of subjects, including the use of Bhopal gas victims in drug trials, the HPV vaccine, irrational / illegal fixed dose combinations, the regulatory mess in India, irrational pricing of medicines, the tremendous brand-generic confusion, and ethical problems in clinical trials. He has described the last as ‘drug neo-colonialism’.

**Dr Jacob Puliyel**

Dr Puliyel is a Consultant Paediatrician and Head of Paediatrics, St Stephens Hospital, Delhi. He is the Chairperson of the Research Ethics Committee, Emmanuel Health Association Group of Hospitals. Currently a member of National Technical Advisory Group on Immunisation (NTAGI) and has also been a member of the Planning Commission Working Group for Drug and Food Regulation for the 12th Five Year Plan. He has peer reviewed journals, over 120 scientific papers and is a reviewer for over ten national and international journals. He is also the winner of the James Flett Gold Medal of the Indian Academy of Pediatrics.

**Dr V.M. Katoch**

Dr Katoch is the Director General, Indian Council of Medical Research and the Secretary, Department of Health Research, MoHFW. Previously, he was the Director of National JALMA Institute for Leprosy and Other Mycobacterial Diseases. He is a Fellow of the National Academy of Science (FNASc), India. He has delivered several Orations, Award Lectures and over 150 Invited Lectures in prestigious institutions and conferences in India and abroad on TB, leprosy, genomics, etc.
Dr Kaushik Sunder Rajan

Dr Kaushik Sundar Rajan is Associate Professor of Anthropology at the University of Chicago. He works on the political economy of the life sciences and biomedicine, with a focus on the United States and India. He is the author of *Biocapital: The Constitution of Postgenomic Life* (Duke, 2006), and editor of *Lively Capital: Biotechnologies, Ethics and Governance in Global Markets* (Duke, 2012). He is currently involved in two research projects. The first studies the Indian pharmaceutical industry and politics surrounding access to essential medicines, following India’s compliance with the World Trade Organisation’s mandated patent regimes; the second follows the establishment of India’s first translational research institute.

Dr Mala Ramanathan

Dr Ramanathan is faculty at the Achutha Menon Centre for Health Science Studies, SCTIMST, Thiruvananthapuram. She completed her Masters in Statistics at the University of Madras, Chennai and obtained her MPhil and PhD in Population Sciences at the International Institute for Population Sciences, Mumbai. She also has a Masters in Medical Anthropology from the University of Amsterdam. She was an Ethics Fellow at the International Bioethics Fellowship Programme at the Department of Population and International Health, Harvard School of Public Health, Boston in 2002-04. She has taught gender in health research and research ethics, both nationally and internationally. Dr Ramanathan has more than 25 publications in national and international peer reviewed journals and edited volumes. She serves on the Editorial Board of the *Indian Journal of Medical Ethics*.

Dr Mohan Rao

Dr Mohan Rao is Professor at the Centre of Social Medicine and Community Health (CSMCH), Jawaharlal Nehru University, New Delhi. A medical doctor specialised in public health, he has written extensively on health and population policy, and on the history and politics of health and family planning. He is the author of *From Population Control to Reproductive Health: Malthusian Arithmetic* (Sage, New Delhi, 2004) and has edited *Disinvesting in Health: The World Bank’s Health Prescriptions* (Sage, New Delhi, 1999) and *The Unheard Scream: Reproductive Health and Women’s Lives in India* (Zubaan/Kali for Women, New Delhi, 2004). With Sarah Sexton, he is editor of *Markets and Malthus: Gender, Health and Population in Neoliberal Times* (Sage, New Delhi, 2010). He is a member of the National Population Commission, and has been on several Working Groups of the National Rural
Health Mission. He has worked on the Committee established by the National Human Rights Commission to examine the two-child norm in population policy. He has been on the Executive Committee of the Centre for Women’s Development Studies. He is also actively involved in the Jan Swasthya Abhiyan.

**Dr Nandini Kumar**

Dr Kumar is graduate and post graduate in Clinical Pathology from Trivandrum Medical College, India. She was involved in medical research in the Gastroenterology Department at Thiruvananthapuram and at Madras Medical College, Chennai. She joined ICMR headquarters in New Delhi as a Senior Research Officer, and became the Programme Officer for Traditional Medicine Research and Bioethics. Currently, after retirement as Deputy Director General Senior Grade, she is involved as an NIH Grantee, in bioethics education through distance learning. She has been instrumental in initiating the first online PG Diploma course in bioethics in India under the ICMR-IGNOU joint initiative. She was also closely involved in the finalisation of the ICMR Ethical Guidelines of 2000 and 2006, including the National Guidelines on Stem Cell Research and Therapy, Guidelines for Research on Ayurveda, Siddha and Unani formulations, and Draft Guidelines on Biobanking, Data Set Protection and Mental Health Research. Presently she is a member of international panel of President Obama’s Commission for Bioethical Issues, Subgroup of National Innovation Council on Pharmaceuticals. She is also a consultant for bioethics issues and traditional medicine research in the country and abroad.

**Mr Parsottam Parmar**

Mr Parsottam Parmar is a social activist for the last 20 years and has worked with various organisations. He is currently the director of RAAH in Ahmedabad, which has been working for the last three years on issues of education and health in the context of displacement. He works specifically in a rights based framework.

**Mr A.K. Pradhan**

Mr Pradhan is from the Central Drugs Standard Control Organisation (CDSCO) and currently, is the Deputy Drug Controller of India, handling the decision of new drugs and clinical trials. Mr Pradhan is a post graduate in Bio Chemistry, and started his career in the department of Pharmacology at the Central Drugs Laboratory in Kolkata where he served for more than 7 years. He joined the CDSCO in 1996. Mr Pradhan has more than 15 years of experience in the regulation of new drugs and clinical trials.
**Ms Rachna Dhingra**

Ms Rachna Dhingra has been working with the survivors of the violations by the Union Carbide and Dow Chemicals in Bhopal in 1984. Over the past ten years, she has been working with the survivors on issues of justice, life and dignity.

**Ms T K Rajalakshmi**

TK Rajalakshmi is a journalist with over 15 years of work experience, currently working as the deputy editor, *Frontline*. She has been writing on health, gender and related issues. She is an executive member of the Centre For Women’s Development Studies, and a former office bearer of the Indian Women’s Press Corps. Her write-up for the Panos fellowship featured in the collection of articles in the *The Unheard Scream: Reproductive Health and Women’s Lives in India* edited by Dr Mohan Rao, (Zubaan/Kali for Women, New Delhi, 2004).

**Ms Rohini Kandhari**

Rohini Kandhari is an M.Phil student at the Centre for Social Medicine and Community Health, Jawaharlal Nehru University and conducted a study of Institutional Ethics Committees in selected hospitals in Delhi.

**Dr Roli Mathur**

Dr Mathur is a molecular geneticist trained at the All India Institute of Medical Sciences, New Delhi. She had received the ‘Young Scientist Award’ in 1998 before joining ICMR in 2001. In the year 2003 she received WHO Fellowship in ‘Bioethics & Ethics Committee Administration’ at USA and was subsequently trained as ‘SIDCER International Surveyor’ of Ethics Committees. She is now a Steering Committee member of FERCAP and member of FERCI. She has been course faculty and surveyor to several ethics trainings and surveys in South East Asia. At the ICMR, she coordinates various activities related to research ethics, including research, trainings, development of ethical guidelines, etc. At present, she is involved with the group drafting the Bill for Regulation of Ethical Issues of Biomedical Research. She is also involved in the functioning of Central Ethics Committee and the ICMR Institutional Ethics Committee.

**Dr Román Pérez Velasco**

Dr Roman Perez Velasco studied Pharmacy at the University of Granada, Spain, and obtained an MSc in Clinical Pharmacy, International Practice and Policy from the London
School of Pharmacy, UK. Before joining HITAP in 2010, he worked in the primary care and hospital sectors in three European countries (Spain, Ireland and the UK), where he became familiar with their health systems and conducted outcomes research. Dr Velasco’s current research focuses on the areas of health screening, chronic disease, emerging health technologies and diseases, and maternal and child health. In addition, he is involved in the development of priority setting criteria and context-specific process guidelines for Health Technology Assessment (HTA) in Thailand. He is interested in evidence synthesis, health economics, outcomes research and policy analysis.

Mr S.(Chinu) Srinivasan

Mr Srinivasan is with LOCOST, a non-profit organisation based in Baroda, that manufactures low-priced formulations and is involved with advocacy on pricing, access and drug regulatory issues. Mr Srinivasan is also an active member of SAHAJ (Society for Health Alternatives, Baroda), All-India Drug Action Network (AIDAN) and Medico Friend Circle (MFC). He has been involved in the movement on rational therapeutics for over three decades and has consistently led advocacy on pro-people drug policy reforms. He has contributed articles and papers on pharma and patent related issues to the Economic and Political Weekly and other journals and has co-authored and edited over half a dozen books, and most recently - Aam Aaadmiyon ke Liye Dawaiyon ki Kitab, October 2011 in Hindi, (The Revised) Lay Person’s Guide to Medicines, LOCOST Vadodara (2006), and Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India, LOCOST/JSS, Vadodara/Bilaspur, 2004.

Dr Samiran Nundy

Dr Nundy was a medical undergraduate in Cambridge and Guy’s Hospital London and then trained, first in Medicine at the Hammersmith Hospital, and later in Surgery at Guy’s, Addenbrookes Cambridge, the Hammersmith and the Massachusetts General Hospital in Boston. He has taught at the Universities of Cambridge, London and Harvard and returned to the All India Institute of Medical Sciences (AIIMS) in 1975, where he eventually became Professor and Head of the Department of Gastrointestinal Surgery. He left AIIMS in 1996 and now heads the GI Surgical department in the Sir Ganga Ram Hospital in New Delhi. His clinical and research interests are in the management of complicated diseases of the liver and pancreas as well as in the quality of Indian medical research and publications. He has been Founder Editor of The National Medical Journal of India and Tropical Gastroenterology and serves on a number of journal Editorial Boards including the British Medical Journal.
Ms Sandhya Srinivasan

Sandhya Srinivasan is a freelance journalist and consultant with Masters degrees in Sociology and Public Health. She has written extensively in academic publications and in the press on current issues in healthcare and medical ethics in India. She is executive editor of the *Indian Journal of Medical Ethics* and consulting editor, public health, for the development website www.infochangeindia.org. Ms Srinivasan was a Panos Reproductive Health Media Fellow in 1998, writing on the infertility industry in India. In 2002, she was awarded the Ashoka Fellowship for work in medical ethics. She is on the editorial board of Developing World Bioethics, faculty of the Centre for Studies in Ethics and Rights, and member of the Network of Women in the Media, India. A collection of papers edited by her, *Making Babies: Birth Markets and Assisted Reproductive Technologies in India*, with Sama, was published by Zubaan in 2010. One of her areas of interest is the ethics of clinical research in India, and she has published articles on this subject in *The Lancet*, *The National Medical Journal of India* and *The Economic and Political Weekly*.

Ms N. Sarojini

N. Sarojini is with Sama–Resource Group for Women and Health, a Delhi based women's organisation. Sarojini has been working as a health activist in the field of women's health for the last 18 years and is actively involved with the women’s movement and health movement. She has been actively campaigning against the two-child norm, population control policies, sex-selective abortions and hazardous contraceptive technologies. She has been involved in advocacy around issues related to Assisted Reproductive Technology, Maternal Health, Health Systems, Unethical Clinical trials, etc. She was involved in Shodhini, a national level research network on traditional medicine and alternative health system for women. She is ex-convener of the Medico Friend Circle and joint convener of the Jan Swasthya Abhiyan.

Dr Satyajit Rath

Dr Satyajit Rath was trained as a physician and pathologist in Pune and Mumbai, and has worked as a researcher in basic immune-biological mechanisms in the UK, USA and, since 1991, at the National Institute of Immunology in New Delhi. He is also interested in issues at the interface of science-society, including education and public policy, and works with organisations such as the Delhi Science Forum (DSF) and the Coalition for Nuclear Disarmament and Peace (CNDP).
Dr Sujith Chandy

Dr Chandy is Professor of Clinical Pharmacology, Christian Medical College (CMC), Vellore. Besides his primary role in teaching pharmacology, he is the coordinator for the pharmacovigilance programme in the hospital. He also holds administrative responsibilities in the pharmacy services. He is a member of the Institutional Review Board, Drugs and Therapeutics Committee, Data Safety Monitoring Committee and Academic Boards. He is also a resource person for ethics, GCP and pharmacovigilance workshops of the institution. Dr Chandy has been active in institutional and collaborative research studies with WHO and Karolinska Institute, Sweden. He is a keen advocate of rational use of medicines, pharmaceutical ethics and pharmacovigilance. Dr Chandy is also a reviewer for Lancet, Indian Journal of Medical Research and other publications.

Dr Sunita S Bandewar

Dr Bandewar has training in Anthropology and Bioethics. She has long standing experience in empirical research in India and abroad and has been engaged in advocacy work. She pursued a post doctoral programme and senior research fellowship in bioethics at the Centre for Global Health, University of Toronto, Canada. She is also involved in teaching and training in Medical Anthropology, bioethics, research methodology and other allied themes in global health and bioethics. She serves on the International Research Ethics Board, Medecins Sans Frontieres (MSF), Geneva, and has served on the National Editorial Board of the Indian Journal of Medical Ethics.

Dr Vasantha Muthuswamy

Dr Vasantha Muthuswamy is a medical graduate and DGO from R.G.Kar Medical College, Kolkata and did her MD in Ob/Gyn from Institute of Obstetrics and Gynaecology, Chennai in 1979. She has served the ICMR in various capacities for 29 years and recently retired as Senior Deputy Director General and Head of Division of Basic Medical Sciences and Division of Reproductive Health and Nutrition. She has played a major role in the Council’s activities in the areas of drug development, including traditional medicine, genetics and genomics, ethics of animal and human experimentation, promotion of research by medical students and development of guidelines to facilitate research in the country. These include the Ethical Guidelines for Research on Human Participants, Guidance Document for Animal Experimentation, Stem Cell Research and Therapy Guidelines, Guidelines for Safety Evaluation of GM Food, Biobanking Guidelines, and Guidelines for Good Clinical Lab. Dr Muthuswamy is member of many national and international ethics committees such as in UNESCO, UNAIDS, HPTN (FHI/NIH), etc. She has conducted a number
of workshops for different stakeholders within India and in more than 25 countries. She is the Founder Member of the Forum for Ethics Review Committees in Asia Pacific and has now taken over as the President.

**Dr Vineeta Bal**

Dr Bal obtained her MD in Microbiology from Haffkine Institute, Mumbai, after completing her MBBS from University of Pune. Her post-doctoral training took place in Haffkine Institute, Mumbai, MRC Tuberculosis and Related Infections Unit, London and Royal Post-graduate Medical School, London. In 1990, she joined as a faculty at the National Institute of Immunology, New Delhi and has worked as an immunologist all her research life with wide ranging interests in the field. Dr Bal has written about and worked towards improving the status of women scientists in India. Her other long-standing focus is on the status of women’s health and she has been associated with Saheli Women’s Resource Centre, Delhi Science Forum and Coalition for Nuclear Disarmament and Peace.

**Adv Vishwas H. Devaiah**

Adv Vishwas H. Devaiah graduated from University Law College, Bangalore with a BAL, LLB degree. He then went on to finish LLM (International Economic Law) from University of Warwick and Ph.D in Law from the University of Liverpool. He has worked as a researcher at the Alternative Law Forum, Bangalore on the Knowledge and Culture Commons Project and also as a consultant with World Health Organisation, 3D (Geneva), Clinton Health Action Initiative (CHAI) and University of Liverpool Management School. He is also the co-founder of Initiative for Medicines Access and Knowledge (I-MAK), New York. He has also taught at University of Liverpool. His research interests include Medical Law, Intellectual Property Law, Law and Politics of Regulation, and Banking Law.
PARTICIPANTS

1. Dr. Amar Jesani
   Indian Journal of Medical Ethics
   Anusandhan Trust
   Sai Ashray, Aaram Society Road, Vakola
   Santacruz East, Mumbai 400055.
   Phone: 022-2666 1176
   Email: amar.jesani@gmail.com

2. Mr. A.K. Pradhan
   Central Drugs Standard Control Organization
   Directorate General of Health Services
   Ministry of Health and Family Welfare
   Government of India
   FDA Bhavan, ITO, Kotla Road, New Delhi-110002
   Phone: 011-23236965/23236975
   Email: dci@nb.nic.in

3. Dr. Amit Sen Gupta
   Delhi Science Forum/AIPSN
   D-158, Lower Ground Floor,
   Saket, New Delhi-110017
   Phone: 011-26862716, 26524342
   Email: ctddsf@vsnl.com

4. Mr. Amitava Guha
   Jan Swasthya Abhiyan (JSA), Delhi
   Email: amitava45@gmail.com

5. Dr. Anand Rai
   Civil Right Activist, Indore
   Email: draanandrai_1977@yahoo.com

6. Dr. Anant Phadke
   Saathi- Cehat
   8, Ameya Ashish Society, Kanak Express Hotel Lane,
   Kothrud, Pune 411038
   Phone - 020 -25460038
   Email: anant.phadke@gmail.com

7. Ms. Anjali Shenoi
   Sama- Resource Group for Women and Health
   B-45, 2nd Floor, Main Road Shivalik
   Malviya Nagar, New Delhi-110017
   Phone: 011-65637632/26692730
   Email: sama.womenshealth@gmail.com
8. Dr. Anju Sharma  
Indian Council of Medical Research (ICMR)  
Post Box No. 4911, Ansari Nagar, New Delhi  
Email: anjusharma@gmail.com

9. Mr. Ankur Paliwal  
Down To Earth  
Society for Environmental Communications  
41, Tughlakabad Institutional Area  
New Delhi - 110062,  
Phone No: 91-11 29955124, 29956110,  
Email: ankur@cseindia.org

10. Mr. Antony Kurien  
Sama- Resource Group for Women & Health  
B-45, 2nd Floor, Main Road Shivalik,  
Malviya Nagar, New Delhi-110017  
Ph: 011-65637632/26692730

11. Dr. Arun Bhatt  
Clininvent Research Pvt. Ltd.  
A-103, Everest Chambers  
Marol Naka, Andheri - Kurla Road  
Andheri (E), Mumbai - 400 059  
Phone: 022 22-6781 8600  
Email : arunbhatt@clininvent.com

12. Mr. Ashok Yadav  
Sama- Resource Group for Women & Health  
B-45, 2nd Floor, Main Road Shivalik,  
Malviya Nagar,  
New Delhi-110017  
Ph: 011-65637632/26692730

13. Dr. Axel Harneit Sievers,  
Heinrich Böll Foundation  
C-20, Qutab Institutional Area,  
New Delhi - 110 016  
Phone: +91 11 26874624  
Email: axel.harneit-sievers@hbfasia.org

14. Ms. Brinda Karat  
AIDWA/ Ex Member of Parliament Rajya Sabha  
A.K. Gopalan Bhawan,  
27-29, Bhai Vir Singh Marg,  
New Delhi 110 001  
Tel. (91-11) 23344918, 23363692  
Email: brinda@cpim.org, cc@cpim.org
15. Dr. P.M. Bhargava
Anveshna
H.No. 2-16-137 (Plot#70)
Road #3, Prashanthi Nagar
Uppal, Hyderabad-500039
Phone: 040-27200868
Email: bhargava.pm@gmail.com

16. Ms. Beenu Rawat
Sama- Resource Group for Women and Health
B-45, 2nd Floor, Main Road Shivalik
Malviya Nagar,
New Delhi-110017
Phone: 011-65637632/26692730
Email: sama.womenshealth@gmail.com

17. Ms. Bhawna Rawat
Sama- Resource Group for Women and Health
B-45, 2nd Floor, Main Road Shivalik
Malviya Nagar,
New Delhi-110017
Phone: 011-65637632/26692730

18. Dr. Chandra M. Gulhati
Monthly Index of Medical Specialties (MIMS)
A.E. Morgan Publications (India) Private Limited
503, Mansarover, 90 Nehru Place, New Delhi - 110 019
Tel.: +91 11 41014693, +91 11 26234875
Email: info@mims-india.com

19. Ms. Deapica Ravindran
Centre for Studies in Ethics and Rights
501, Dalkhania House, B Wing
Behind State Bank of India,
Nehru Road,
Vakola Pipe Line, Santacruz (East),
Mumbai – 400 055
Email: deapica@gmail.com

20. Dr. Dinesh Agarwal
National Programme Officer (RH)
UNFPA
55, Lodhi Estate
New Delhi – 110003
Tel: +91 11 42225030
Mobile: +91 9868884942
Email: agarwal@unfpa.org
21. Ms. Deepa Venkatachalam
Sama- Resource Group for Women and Health
B-45, 2nd Floor, Main Road Shivalik
Malviya Nagar,
New Delhi-110017
Phone: 011-65637632/26692730
Email: sama.womenshealth@gmail.com

22. Mr. G.S. Mudur
Telegraph
Express Building, 3rd Floor,
9/10 Bahadur Shah Zafar Marg,
New Delhi 110 002,
Phone : +91-11-23702170-79,
Email: gsmudur@gmail.com

23. Dr. G.D. Ravindran
St. John’s Medical College, Bangalore
Email: gdravindran@gmail.com

Jananeethi Institute,
Jananeethi Campus, Mullakkara,
Mannuthy Post, Thrissur,
Kerala- 680651
Phone:0487-2373479 / 2373281
Email: gpneethi@sancharnet.in; jananeethi@jananeethi.org

25. Ms. Ishita Sharma
Sama- Resource Group for Women and Health
B-45, 2nd Floor, Main Road Shivalik
Malviya Nagar,
New Delhi-110017
Phone: 011-65637632/26692730

26. Dr. Eswara Reddy
Assistant Drug Controller (I)
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi-110002
Phone: 011-23236965/23236975
Email: dci@nb.nic.in
27. Dr. Joe Varghese  
Christian Medical Association of India (CMAI)  
Plot no 2, A-3 Local Shopping Centre  
Janakpuri, New Delhi 110 058, India  
Phone: 011 11 255 9999 1/2/3  
Email: jvarghese@cmai.org

28. Dr. Jacob Puliyel  
G-1 Old Administration Block  
St Stephens Hospital, Tis Hazari, Delhi 110054  
Email: jacob@puliyel.com

29. Dr. Kabir Sheikh  
Public Health Foundation of India (PHFI)  
ISID Campus,  
4 Institutional Area  
Vasant Kunj  
New Delhi – 110070  
Phone: 01149566000  
Email: kahir.sheikh@phfi.org

30. Dr. Kaushik Sunder Rajan  
University of Chicago  
Email: ksunderr@uchicago.edu

31. Mr. L.C. Goyal,  
Additional Secretary and Director General (CGHS)  
Ministry of Health and Family Welfare  
Nirman Bhawan  
New Delhi -110001  
Email: lc.goyal@nic.in

32. Dr. Mala Ramanathan  
Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST),  
Thiruvananthapuram, Kerala  
Phone: 0471-2443152, 2443085  
Email: mala@satimst.ac.in

33. Dr. Madhu Sharma  
Indian Council of Medical Research (ICMR)  
Post Box No. 4911, Ansari Nagar, New Delhi  
Email: madhu.m34in@gmail.com
34. Dr. Mira Shiva  
Initiative for Health & Equity in Society  
All India Drug Action Network  
A-60, Hauz Khas  
New Delhi - 110 016  
Phone: 91-11-26512385  
Email: mirashiva@gmail.com

35. Dr. Mohan Rao  
Centre of Social Medicine and Community Health  
Jawaharlal Nehru University  
New Delhi-110067  
Phone: 011-26742730  
Email: mohanrao2008@gmail.com

36. Ms. Mohuya Chaudhuri  
NDTV  
Phone: 011 26446666  
Email: mohuya.chaudhuri@gmail.com

37. Ms. Neha Madhiwalla  
Centre for Studies in Ethics and Rights  
501, Dalkhania House, B Wing  
Behind State Bank of India, Nehru Road,  
Vakola Pipe Line, Santacruz (East),  
Mumbai – 400 055  
Phone: 022 - 2668 1568  
Email: nmadhiwala@gmail.com

38. Dr. Nandini K. Kumar  
Former Deputy Director General Sr. Grade Investigator NIH project  
National Institute of Epidemiology  
R 127, 3rd Avenue, TNHB  
Ayapakkam  
Chennai 600077  
Phone: 044 26136214  
Email: nandkku@yahoo.com

39. Mr. Parsottam Parmar  
RAAH  
4 Indira Park Society  
Opposite 10D  
Beema Yojana Dawa Khana  
Kalapi Nagar  
Ahmedabad -380016  
Email: rahgujarat@yahoo.com
40. Ms. Pooja Sharma
   Medanta
   Email: poojasharma@medanta.org

41. Ms. Preeti Nayak
   Sama- Resource Group for Women and Health
   B-45, 2nd Floor, Main Road Shivalik
   Malviya Nagar,
   New Delhi-110017
   Phone: 011-65637632/26692730
   Email: sama.womenshealth@gmail.com

42. Ms. Rachna Dhtagra
   Bhopal Group for Information & Action, Bhopal
   Email: rachnya@gmail.com

43. Ms. Rajalakshmi T.K
   Frontline
   Email: tk.rajalakshmi@gmail.com

44. Dr. Ravi Vaswani
   7A Delta Court, SL Mathias Road
   Mangalore 575001 Karnataka
   Email: mirdad365@gmail.com

45. Mr. Ranjit Devraj
   Inter Press Service News Agency
   Email: ranjit.devraj@gmail.com

46. Dr. R.K. Pal
   National Health Systems Resource Centre (NHSRC)
   Munirka, New Delhi
   Phone: 011-26108982/ 83/84/92/93 Extn 227
   Email: palrk2002@gmail.com

47. Ms. Rohini Kandhari
   21, NRI Complex, 2nd Floor, Greater Kailash -IV,
   Mandakini, New Delhi – 110019
   Email: rohini22@gmail.com

48. Dr. Roli Mathur
   Indian Council of Medical Research (ICMR)
   Post Box No. 4911, Ansari Nagar, New Delhi
   Email: rolimath@icmr.org.in
49. Mr. Román Pérez Velasco  
Health Intervention and Technology Assessment Program (HITAP)  
6th Floor, 6th Building, Department of Health, Ministry of Public Health  
Tiwanon Rd., Muang, Nonthaburi 11000, Thailand  
Phone: +66 (02) 5904549, +66 (02) 5904374, +66 (02) 5904375  
E-mail: roman.p@hitap.net

50. Ms. Salla Sariola  
University of Durham  
Email: salla.sariola@gmail.com

51. Dr. Samiran Nundy  
Consultant Gastro- Intestinal surgeon,  
Sir Ganga Ram Hospital, Rajinder Nagar,  
New Delhi 110060  
Phone: 011 25750000,42254000  
Email: snundy@hotmail.com

52. Dr. Santanu K Tripathi  
Department of Clinical & Experimental Pharmacology  
Calcutta School of Tropical Medicine  
108 Chittaranjan Avenue  
Kolkata 700 073  
Email: tripathi.santanu@gmail.com

53. Mr. S (Chinu) Srinivasan  
Low Cost Standard Therapeutics  
1st Floor, Premanand Sahitya Sabha  
Dandia Bazar,  
Baroda-390 001  
Gujarat.  
Phone: 0265 2413319  
Email: sahajbrc@gmail.com

54. Ms. Sandhya Srinivasan  
Indian journal of Medical Ethics  
8, Seadoll  
54, Chimbai Road, Bandra (West)  
Mumbai- 400050  
Phone: 022-26400607  
Email:sandhya_srinivasan@vsnl.com
55. Dr. Satyajit Rath  
National Institute of Immunology (NII)  
JNU Complex, Aruna Asaf Ali Marg,  
New Delhi, 110070  
Phone: 011 26717016  
Email: satyajit@nii.res.in

56. Ms. Sarla Balachandran  
Council of Scientific and Industrial Research  
Anusandhan Bhawan,  
2 Rafi Marg, New Delhi-110001  
Phone: 01123710138, 23710144  
Email: sbalachandaran@csir.res.in

57. Ms. Sarojini N  
Sama- Resource Group for Women and Health  
B-45, 2nd Floor, Main Road Shivalik  
Malviya Nagar,  
New Delhi-110017  
Phone: 011-65637632/26692730  
Email: sama.womenshealth@gmail.com

58. Ms. Shalini Yog  
Programme Co-ordinator  
Heinrich Böll Foundation  
C-20, Qutab Institutional Area,  
New Delhi - 110 016  
Phone: +91 11 26874624  
Fax: +91 11 26962840  
Email: shalini.yog@in.boell.org

59. Ms. Shelley Dhar  
The Action Northeast Trust (ANT)  
Udangshri Dera  
Rowmari, via Bongaigaon  
Distt Chirang (BTAD)  
Assam- 783380  
Phone: 03664293802/293803  
Email: shelleydhar@gmail.com

60. Ms. Shelley Saha  
Centre for Health and Social Justice  
Basement of Young Women's Hostel No 2 (Near Bank of India)  
Avenue 21, G Block, Saket  
New Delhi-110017  
Ph: 011-26511425, 26536163  
Email: shelley@chsj.org
61. Dr. Sunita Bandewar
   C-5, Mantri Avenue-I,
   Panchavati, Pashan Rd
   Pune, 411008, Maharashtra
   Phone: +91 20 25888479
   Email: sunita.bandewar@utoronto.ca

62. Dr. Sujith Chandy
   Clinical Pharmacology Unit
   CMC Hospital, Scudder Road
   Vellore, Tamil Nadu – 632004
   Email: sjchandy@gmail.com

63. Ms. Susheela Singh
   Sama- Resource Group for Women and Health
   B-45, 2nd Floor, Main Road Shivalik
   Malviya Nagar,
   New Delhi-110017
   Phone: 011-65637632/26692730
   Email: sama.womenshealth@gmail.com

64. Ms. Tarang Mahajan
   Sama- Resource Group for Women and Health
   B-45, 2nd Floor, Main Road Shivalik
   Malviya Nagar,
   New Delhi-110017
   Phone: 011-65637632/26692730
   Email: sama.womenshealth@gmail.com

65. Dr. V.M. Katoch
   Secretary (Department of Health Research & Director General)
   Indian Council of Medical Research (ICMR)
   Post Box No. 4911, Ansari Nagar, New Delhi
   Email: secydhr@icmr.org.in, dg@icmr.org.in

66. Dr. Vasantha Muthuswamy
   Senior Deputy Director General (Retd.)
   Indian Council of Medical Research (ICMR), New Delhi
   Presently,
   A, 101, Manchester Regent
   Avinashi Road, P.N.Palayam,
   Coimbatore – 37
   Email: vmuthuswamy@hotmail.com
67. Dr. Vina Vaswani  
Centre for Ethics, Yenepoya University  
Professor & Head, Dept of Forensic Medicine & Toxicology  
Yenepoya Medical College, Mangalore 575018  
Cell: +919449003989  
Email: bioethics@yenepoya.edu.in

68. Dr. Vineeta Bal  
Saheli Women’s Resource Centre  
Above Unit 105-108  
Defence Colony Flyover Market  
New Delhi-110024  
Email: vineetabal@yahoo.com

69. Dr. Vishwas H Devaiah  
Assistant Professor,  
No.12, Ambedkar Bhavan,  
West Bengal University of Juridical Sciences,  
LB Block, Sector III, Salt Lake City,  
Kolkata-700098, West Bengal  
Email: vishwas123@gmail.com

70. Ms. Vrinda Marwah  
Sama- Resource Group for Women and Health  
B-45, 2nd Floor, Main Road Shivalik  
Malviya Nagar,  
New Delhi-110017  
Phone: 011-65637632/26692730