Third
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Contemporary Issues in Health and Social Sciences
Instituted by Anusandhan Trust

CLINICAL TRIALS AND HEALTHCARE REGULATION IN INDIA

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Anusandhan Trust has instituted the Krishna Raj Memorial Annual Lecture Series on Contemporary Issues in Health and Social Sciences to honour the intellectual and academic traditions that Krishna Raj set in place, and in his memory. This is a humble tribute to the memory of the visionary editor of the *Economic and Political Weekly* (EPW)

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Preface

Clinical research is an important aspect of universalising healthcare, enabling the development of better drugs, tests, vaccines, devices, surgical procedures and other medical interventions and protocols for their safer and more rational use. However, today it is viewed merely as a business investment with high returns. This view has been strengthened by the global trend to marginalise public sector involvement in drug development, a trend that has reduced the potential for non-profit use of the gains of research. Moreover, the growth of clinical research as a global industry has not been matched by an increase in expertise in regulating the complex arrangements that have emerged through the process of outsourcing and off-shoring clinical trials.

In the recent past, attention has focused on the ethical, legal and social issues in the conduct of clinical trials. This is largely based on reports of people being harmed when participating in a trial. While such violations in clinical research must be highlighted and action taken on them, they cannot be prevented without regulation and equity in the healthcare sector as a whole.

With the commodification of healthcare, in which the dominant mode of delivery is by fee-for-service, most healthcare encounters are negotiated by individual patients with individual providers or institutions. The poor, who use free or subsidised care in the public sector, are viewed as recipients of welfare rather than as citizens with rights. Issues such as accountability and human rights do not enter the discourse. It is not surprising that the machinery required for regulation, such as comprehensive legislation, an adequate administrative setup and budgetary support, is largely missing in India. Thus, even when they are noted, individual violations are treated as random, ill-intentioned actions of individuals. This obscures the role played by the system in creating the conditions that make patients and research participants vulnerable.

The theme for this seminar was chosen in order to initiate a discussion on clinical trials against the background of governance of the healthcare sector. This meeting, organised by the Centre for Studies in Ethics and Rights (CSER) and the *Indian Journal of Medical Ethics*, is part of a long-term programme to use research, training and public engagement to develop a better understanding of the social and ethical dimensions of clinical research.

This report summarises the presentations and discussions at the seminar. It starts with an overview of ethical concerns in clinical research from the perspectives of Indian activists and those in the West. It then presents the summary findings of an investigation into four trials. Important issues identified in the ensuing discussions are given: the nature of consent from vulnerable groups, the impact of incentives and inducements, and the ethics of placebo controlled trials. The third part of this meeting focused on regulation: in healthcare research, the manufacture of medical devices, and the provision of health services. Presentations were made by a researcher studying ethics committees, a drug manufacturer, and a health activist. Drawing the links between these sections… one can see the interrelatedness of ethics, equity and governance.

Neha Madhiwalla
coordinator, CSER

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The context of clinical research in India

The seminar began with an overview of the concerns emerging about the growth of the international clinical research industry.

Research turns commercial

Presenting the Indian scenario, **Amar Jesani** noted that between 50,000 and 75,000 clinical trials are conducted annually across the world. In India, where a significant proportion of these trials has been run, clinical research has always been viewed with suspicion because of reports of breaches of ethical norms. In fact, as far back as in the 1980s and 1990s, government-sponsored trials, particularly for contraceptives, have faced public interest litigation for violating participants' rights.

New problems arise as research gets increasingly commercialised. Jesani suggested that drug companies and lawmakers have a greater interest in safeguarding patent rights than protecting participants and host populations. India offers business opportunities because of the availability of cheap medical labour, a diverse disease profile and a large patient population which has not received treatment. This has led to the emergence of contract research organisations (CROs) which facilitate clinical research and ensure that legal requirements are met so that companies' interests are protected and their business needs ? minimising costs and increasing profits ? met.

Jesani emphasised that clinical trials are necessary and they should not be viewed as inherently unethical; the environment must be created in which they are conducted ethically, in a setting where patients are assured of the right to healthcare regardless of their decision on whether or not to participate in a trial.

Further, transparency and public accountability are needed so that the public can play the role of monitor. The public has a right to information about the actual conduct of the trial and observations related to it. At present, only some details about the research proposal are available in the public domain.

There are also larger questions of justice related to the relevance of clinical research and access to the benefits of research. The weak Indian disease surveillance system provides little empirical evidence to establish the relevance of a particular study to the country's health needs. Drugs or other interventions developed through research may be expensive and therefore unavailable to the public. For example, though India was a site for research on the HPV vaccine for protection against cervical cancer, this vaccine is priced at $250, putting it out of the reach of virtually all women in India. There is no provision to ensure that participants, communities or countries have access to the outputs of research after the trial.

Jesani concluded with a summary of the ethical requirements of clinical trials: participants must be protected, exploitation must be prevented, and the benefits of clinical research must be distributed justly. Comprehensive information should be made available in the public domain, in a systematic format, so that we can better judge the relevance and ethical conduct of clinical research in India.

"Their bodies, our drugs"

Annelies den Boer provided a perspective from western Europe where most major multi-national drug companies are located. She noted that companies seeking marketing approval for their drugs in the European Union (EU) are off-shoring the trials for this approval to low income countries. The concerns arising from this trend had led to groups such WEMOS to focus their attention on it. She reiterated some of the factors that make India attractive for drug companies as a site for clinical trials. Not only is regulation lax, trials can be done "cheap, fast and easy": medical labour is cheap and participant recruitment is fast and relatively easy because of the large patient population, many of whom are poor and can be induced to participate in a trial to obtain some treatment.

Business opportunities take precedence over the protection of participants, said den Boer. For example, the former chief executive officer of the multi-national Glaxo Smith Kline (GSK) was quoted in *Fortune* magazine as saying that a trial in Lithuania costs $3,000 per participant compared to $30,000 in the United States. According to a McKenzie report, the faster subject recruitment in developing countries reduces the time required to complete the trial and get the drug to the market. There are also fewer

bureaucratic hurdles here. Finally, drug trials on treatment naïve patients provide "clean" data and there is no need to adjust for the effect of other medications taken by the patient.

den Boer provided some figures on trends in off-shoring. While there is no standard system for registering trials conducted outside the United States, drug companies have stated that between 30% and 70 % of company-sponsored clinical trials are conducted in low income countries. In 2004, GSK conducted 29% of its trials outside the United States and the EU and projected that the number would rise by 50% in 2006. Wyeth off-shored 50% of its clinical research in 2004 and projected that this would go up to 70% in 2006. The Drugs Controller General of India (DCGI) has stated that the number of CROs registered with the US Food and Drugs Administration (US FDA) and active in India went from 60 in 2000 to 150 in 2006.

Trials submitted to the European Medicines Authority (EMEA) are supposed to follow the Declaration of Helsinki, which lays down standards for the protection of human subjects in clinical research. However, ethical violations have been found in several trials conducted for EMEA approval. Most often, proper informed consent was not obtained; the informed consent form was not available in the local language or participants were not aware that they were in a clinical trial. Provisions had not been made for post-trial benefits. Such violations were possible because the authorities responsible for approving drugs and issuing licenses are only interested in efficacy and safety data and not the ethics of the research.

Drugs with high risk profiles were usually conducted in low income countries. Low risk drugs trials were conducted in high income countries. The drug company AstraZenaca publicly declared that as institutional ethics committees in Europe did not allow high risk protocols, it was forced to off-shore its trials to low income countries.

It was found that guidelines on incorporating ethics in the registration process are vague though drug approval administrations are becoming more convinced that compliance with ethics guidelines should be part of the registration process. This is important as pharmaceutical companies will start taking ethics seriously only when unethical conduct has business and financial implications. She said that advocacy groups in Europe are

lobbying with the legislature and seeking political support in Europe to make ethics a priority, both at the European Union and at the national levels.

den Boer concluded that there was a need for greater collaboration between groups based in developing and developed countries to enable better public monitoring of clinical trials, particularly in India, Eastern Europe and Latin America. These regions had weak institutional structures for monitoring the conduct of clinical trials; their laws were inadequate and enforcement weak. As a result, they were ill-equipped to fulfil their responsibility to protect human subjects. WEMOS planned to install a clinical trial watch to monitor clinical research in India and Latin America.

An investigation of four clinical trials in India

A key session in the seminar was the discussion of an investigation of clinical trials conducted by Sandhya Srinivasan and Sachin Nikarge for the Centre for Studies in Ethics and Rights and WEMOS. The objective of the investigation was to identify ethical concerns in clinical trials sponsored by multi-national pharmaceutical companies and conducted in India but for marketing approval in the European Union. The investigation findings were presented by **Sandhya Srinivasan.**

The presentation started with giving the general context of clinical trial regulation and the practices of CROs. Since 2005, the government has been relaxing regulations related to clinical research and providing incentives to conduct clinical trials in India. The phase lag between clinical trials elsewhere and in India has been dropped and the DCGI has indicated that permission will soon be granted to conduct Phase 0 and Phase 1 trials in India for drugs being developed elsewhere. There is talk of establishing an export promotional council for clinical research as an industry in India. The clinical trials industry has been permitted to provide large financial incentives to health providers who recruit patients. The government has also turned a blind eye to the fact that CROs are identifying potential patients by holding “diagnostic camps” and by gaining access to hospital databases.

A study of trial participants, conducted by a CRO and presented at a clinical research conference, found that in **97%** of cases, their primary physicians either recruited them directly into the trial or referred them to the research investigator. In other words, healthcare providers are the main channel for participant recruitment. This can conflict with their duty to provide care. There is also a clear possibility that doctors will exploit the unequal patient-provider relationship.

The investigation covered four trials from a selection of trials with sites in India which were used for EMEA approval. They were chosen because

they involved vulnerable populations and also posed serious risks to the participants. They included participants who had a serious illness. The trials were: a phase 2 trial of lapatinib (marketed by Glaxo Smith Kline) for advanced HER2 positive breast cancer that tested a treatment that is beyond the reach of the majority of Indians; and three psychiatric drug trials (risperidone by Johnson & Johnson and quetiapine by Astra Zeneca) that involved patients whose ability to give consent, or withdraw consent once given, was potentially impaired.

The investigation suggested that patients would want to enter these trials in order to get access to free treatment or better treatment that they could not otherwise afford. This treatment would have served as an inducement to participate in the trial. In fact, the researchers interviewed justified the selection of poor participants because they felt that it provided them the opportunity to receive some care and treatment.

The ethical concerns identified in each of the trials by the investigation were presented.

The breast cancer drug trial required patients with advanced breast cancer who had not received the standard treatment. Standard treatment for this type of breast cancer costs Rs 1.2 lakh for a month's treatment and is to be taken for as long as it works. For many women, entering the trial of an experimental drug could represent their only opportunity for some kind of treatment. The drug company's response to questions suggests that women for whom the experimental drug stopped working were not given the standard treatment. The trial violated regulations in place at the time it was conducted: before January 2005, the "phase lag" rule required that phase 3 trials should have been completed elsewhere before phase 2 trials could be conducted in India. The phase 2 lapatinib trial did not follow this requirement. Finally, the approved drug is priced out of reach of the majority of Indians.

The placebo-controlled trial for risperidone to treat acute mania was conducted exclusively in India. Data from this trial were used to obtain USFDA approval for the drug's use in acute mania. Participants in the placebo arm were deprived of effective and available drugs that were considered to be standard treatment in government hospitals. The patients in this trial were much more seriously ill than a similar risperidone trial in

the US and those receiving placebo would therefore have suffered severe harm.

The placebo-controlled trials of an extended release formulation of quetiapine for schizophrenia caused serious harm to participants by depriving them of an existing effective drug. In one of the trials, a participant in the placebo arm committed suicide though researchers maintained that the death was "unrelated" to trial participation. Clinical pharmacologists stated that there was no scientific justification for placebo controlled trials to test new formulations of an approved drug.

It was found that little information about the conduct of these trials was available in the public domain. Few of the pharmaceutical companies who were contacted for information on the trials responded and all of them refused to divulge information about the numbers and characteristics of trial participants recruited at each site. Only one institution provided the investigators with a copy of the informed consent form and the IEC certificate.

This investigation also indicted the functioning of regulatory authorities and the ethics review process. All four trials were reviewed by local ethics review committees and conducted with regulatory approval.

The government policy to encourage "clinical trial tourism" in India, without first putting in place mechanisms to protect trial participants and the community, is of great concern.

Commentaries

Soumitra Pathare commented on informed consent and the role of ethics committees in these trials. He stated that no one with a reasonable amount of information about the psychiatric drug trials would volunteer to participate in them.

The details given on the risperidone and quetiapine trials indicate that participants did not have the capacity to consent.

Informed consent: protecting vulnerable research participants?

In psychiatry, obtaining informed consent is of particular concern as patients may lack insight into their illness. For instance, patients with

severe mania have an impaired understanding of risk, making them more likely to be more reckless, which they regret on returning to stability, and consent obtained from them in such circumstances cannot be considered valid.

Proxy consent is substituted decision making by a family member or by someone with the best interests of the consentee. A key issue in research involving psychiatric patients is the validity of proxy consent obtained from a caregiver. There are established tests to assess whether the proxy consent is reliable but there is no indication that either assessment was carried out in the trials that were investigated. Indeed, most trials involving participants with mental disorders will not specify the basis on which proxy consent is given.

Pathare spoke about the notion of consent as contained in various legal provisions and guidelines. Indian law is silent on the subject of proxy consent, but it has been customary practice to allow proxy consent. However, human rights documents, such as the International Covenant for Protection of Civil and Political Rights and the Convention on Rights of Persons with Disabilities, prohibit the recruitment of people in medical experimentation without their consent and do not provide for the alternative of surrogate consent. As India has ratified both these instruments, they have the legitimacy of law in this country.

In contrast, non-binding guidelines such as the UN Principles for Protection of Persons with Mental Illness and Improvement of Mental Health Care permit surrogate consent when there is supervision by an independent review committee. Technical standards, which include the CIOMS Guidelines, allow for surrogate consent if the research could not be equally effectively conducted with the participation of those who are competent to give consent, and if the research is conducted for the purpose of obtaining knowledge relevant to the health needs of the concerned persons with mental or behavioural disorders. However, these documents dilute these safeguards by giving primacy to local law, even permitting the over-riding of the objections of the ill person in accordance with local law.

The Declaration of Helsinki permits proxy consent and the involvement of legally incompetent persons in research with the condition that the research should involve minimal risk and burden. However, both the DoH

and the CIOMS guidelines fail to define what is meant by a "legally authorized representative", leaving it to the researcher's discretion. Pathare held that the DoH, which is quoted by all pharmaceutical companies conducting clinical trials in India, offers the least protection to participants with mental disorders.

Incentives and inducement

The investigation found that investigators routinely received financial and other incentives to recruit trial participants. According to the Declaration of Helsinki and the ICMR guidelines, funding of any kind represents conflict of interest that must be declared to potential trial participants as well as the ethics committee reviewing the proposal. Such a declaration does not seem to be routine practice in India.

The ICMR guidelines also prohibit, as "undue inducement", any payment to participants other than travel costs and lost wages, though the investigation indicated that such inducements are often offered. In the discussion following the presentation, it was suggested that payment was legitimate as the participant bears the risk but reaps the minimum benefits, especially when compared to what the drug companies gain and the "incentives" received by investigators. This view was contested by others.

Since vulnerable participants are involved in clinical research, ethics committees must be independent and able to provide adequate oversight. However, many ethics committees are controlled by the institution and cannot act independently. Most of them are untrained and may not be competent to assess ethical and scientific issues. There is also no clarity about the extent of their responsibility and their accountability. Can they be taken to court for failure to perform their fiduciary duty? There is no regulation of the ethics committees themselves.

Pathare concluded with a comment on the government regulatory authority, Drugs Controller General of India (DCGI). The DCGI is at present unable to ensure that a trial is conducted ethically. At present, there is no additional protection mandated for ensuring ethical conduct, for example related to seeking informed consent in trials involving vulnerable populations such as persons with mental illness. The ICMR's clinical trial registry, an online database of ongoing clinical trials, can bring about some transparency.

Placebo-controlled trials for serious disease conditions

The use of placebo-controlled trials was discussed in detail. The latest revision of the Declaration of Helsinki re-asserts that the use of placebo is acceptable only in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and patients who receive placebo will not be subject to any risk of serious or irreversible harm.

Drug companies benefit from using a placebo-controlled trial as it requires a smaller sample size to show a drug's efficacy. An active controlled trial requires a larger sample size, will take longer to complete and cost more. The scientific merits of a placebo control have also been questioned as it only proves that the new drug is better than a sugar pill. To justify the introduction of a new drug, it should be shown to be more effective than existing, effective drugs.

Finding a middle ground

In her comments, **Urmila Thatte** stated that there were certain situations in which a placebo controlled trial was necessary for methodological reasons. The quetiapine trials did not meet this standard.

Thatte concurred that there was a serious possibility of exploitation in clinical research but also pointed out that clinical researchers would find it impossible to conduct research if one insisted on ideal conditions. She appealed for a sense of balance, which would ensure that clinical research was suitably regulated, but not made impracticable by the enforcement of formal mechanisms. What was needed was dialogue between the various stakeholders, including clinical researchers, to facilitate good research. Activism alone may not be effective as it would close doors for discussion, thereby isolating the various stakeholders.

Building an environment of good governance

The final session of the seminar was a panel discussion on regulation in the healthcare sector. Three panellists were invited to reflect on the implications, for clinical research, of regulation of research through ethics committees, regulation of drug production and regulation of healthcare services, drawing out the implications for clinical research.

Are internal ethical safeguards effective?

Mala Ramanathan began by outlining the existing framework for the establishment and effective functioning of institutional ethics committees (IECs). The IEC has become more important with the amendment of Schedule Y of the Drugs and Cosmetics Act, 1940, which allows for trials to be conducted in India concurrently with trials abroad. This has prompted a spurt in the number of clinical trials conducted in India, particularly those sponsored by international pharmaceutical companies. It has also increased the risks faced by participants here, as published results from earlier phase trials of the drug are not available. Moreover, the decisions of other IECs which could form precedents are not available.

The enhanced role of the IEC has to be viewed against the background of increasing off-shoring of clinical research to India and the absence of any substantial strengthening of systems for monitoring and protection here.

One positive step is the institution of Good Clinical Practice (GCP) guidelines which aim to standardise clinical practice across the board. IECs and the DCGI require that the investigators working in clinical trials be trained in GCP. However, this has not made the task of ethical review easier for the IECs.

While all IECs are expected to protect participants, an unwritten objective of the IEC is to protect the institution. This is not unjustified as, indirectly, this would also ensure protection for the researchers. While some IECs

have an explicit mandate of protecting researchers, the ICMR guidelines restrict themselves to protecting trial participants.

Pressure from the International Committee of Medical Journal Editors has substantially increased the number of registrations but has not affected the registration of trials which the investigators do not wish to publish. Most recently, the DCGI has made it compulsory for all trials conducted in India to be registered on the CTRI database. Before the DCGI's announcement, a few individual IECs had made registration with CTRI mandatory; the registration number needs to be submitted to IEC before the initiation of the study.

One common problem faced by IECs is their inability to follow up on trials to ensure that they are conducted ethically. IEC members have full-time jobs and serving on an IEC is an additional, voluntary task. The phenomenal increase in the number of trials has overtaken the ability of IEC members to regulate them. The IEC does not have the time or the money to meet every day and it is difficult to assemble members for a meeting when they are based in different parts of the country. Further, important decisions cannot be taken via email; physical meetings are necessary.

The globalisation of research has also added other challenges. CROs are often based in western countries and their data safety and monitoring board (DSMB) can be slow to respond. This is changing with the emergence of Indian CROs in cities such as Mumbai and Bangalore.

Another important issue was related to IEC members' competence to review. Currently, some online training courses are available, but they provide only the bare minimum. It is difficult to get external members find time to attend training but they are the mainstay of the institutional ethics committee.

Essentially meagre funds lead to a lack of investment in staff, infrastructural requirements of IECs and their training.

What IECs can do, given these constraints? There is a need to work out innovative solutions for problems. For example, IECs need to monitor serious adverse events but members are not necessarily from the medical

profession and are not always able to evaluate the data that they receive. They need to make judgements about the completeness of the reports and assess the seriousness of the event. One IEC has developed reporting criteria. A site-based DSMB has been established which reviews the data and reports to the IEC. This IEC has also appointed a local insurance agent to provide insurance against harm to participants in the clinical trial.

IECs expect that researchers will self-regulate and do not see themselves as performing the role of policing researchers. However, this is not communicated effectively and researchers within the institution view the IEC as a policing body. This problem is compounded by the fact that there is no skill development among researchers in ethics.

There is a lack of clarity about many ethical issues. For example, while IECs require that post trial benefits be mentioned in the protocol, ambiguities exist about the nature of post trial benefits and whether it should always be interpreted as access to drugs. If post trial benefits are interpreted as access to free treatment, there is no clarity about the type and duration of treatment that should be committed. These questions can not be addressed adequately through existing ICMR guidelines either.

Ramanathan concluded with a proposed agenda of actions to improve the functioning of IECs. They should be regulated through enhanced accountability. Also, there is a need to reduce risks to IEC members through insurance mechanisms, which are not currently available. There is a need to network across IECs in order to share information about what works and what does not, find ways of sharing information that is easily accessible, and build skills for ethical review.

The manufacturer's ethical concerns

S Srinivasan spoke about legal and ethical issues in the regulation of drug and device production.

In drug and device production, there are three broad areas of concern – the point of view of the manufacturer, the regulator and the consumer. Although a lot has been said about consumers, there has not been much discussion on the concerns of manufacturers and regulatory agencies.

When exploring drug and device production, the ethical manufacturer has several worries. Is the drug rational and essential? Is it better than existing alternatives in terms of safety, efficacy and costs to the patient? Is the manufacturer promoting evidence-based medicine? Is the manufacturer selling an unnecessary fixed dose combination to help his bottom line? Manufacturers also want to be assured about the source of raw materials to ensure quality control.

These questions are as valid for ayurvedic and herbal medicines as for allopathic drugs. The approval of many unscientific formulations is cause for worry.

Other questions that an ethical manufacturer would ask are: What is a reasonable price for a drug? Has the manufacturer been ethical in marketing to the prescribing doctor and the seller? Is the manufacturer corrupting or "entangling" the medical profession? "Entanglement" takes place in many ways, by accepting or giving direct or indirect gifts leading to inducement. They could include gifts in cash or kind, sponsored vacations, ownership of stock or equity holdings; company funding for medical schools, academic chairs, or lecture halls. Even the best doctors are subject to bias because of these kinds of inducements. Undertaking paid consultancy work for companies also results in a bias. Membership of company advisory boards as "thought leaders", "speakers", "bureaus" and authoring "ghost-written" articles that get published in esteemed scientific journals are also forms of entanglement in the medical profession.

For professionals, the medical institution needs to reflect on whether there is a system in place to prevent professional staff from being induced by the manufacturer's largesse by putting in regulatory mechanisms – such as a prohibition on accepting promoter's quota shares. Srinivasan has found that this practice is widely prevalent, and none of the stakeholders, including the drug inspectors, think that this is unethical.

Regulators need to reflect on whether they are sufficiently responsive to public complaints related to the manufacture, use and marketing of the drug. Can the public obtain objective information, warnings, alerts on approved drugs easily?

Can the regulatory authority play a role?

From a regulator's standpoint, the DCGI needs to ensure that approvals are quick, objective, and transparent, keeping in mind that the drug should be essential, rational, effective and safe. Regulators need to allow open systems for public inspection, making sure systems are corruption-proof and lobby-proof; they should leave little scope for discretionary behaviour on part the staff. The DCGI must employ only evidence-based medicine in decisions. However, this is not happening. A serious concern from a regulatory point of view is the lack of competent staff to evaluate technical issues.

In the Indian setting, there are no systems to approve the text of information provided to physicians and patients. The USFDA not only approves drugs but also reads and approves the contents of patient package inserts.

Currently, in India, there is no space for a manufacturer to point out misleading drug advertisements and demand action. It is also not clear whether the DCGI itself has mechanisms in place to prevent corruption, for example in the form of inspectors receiving manufacturer's largesse. Srinivasan referred to the practice by manufacturers of giving inspectors shares from the promoter's quota. There is also no alarm raised about the lack of information and transparency about drug approval, quality control and adverse event reporting.

Strengthening regulation of device production

Srinivasan reported on efforts to set up a separate regulatory framework for medical devices production in the form of a medical devices regulation bill (MDRA).

At present, devices are included in the definition of a "drug" in the Drugs and Cosmetics Act. This was explicitly stated by the Bombay High Court where it stated that drug eluting stents should be treated like any other drug, and brought under price control, as is done in other countries. So a new device should meet the same requirements as for a new drug; proof should be submitted it is not inferior to the existing one. Only then can permission for marketing it be granted.

The MDRA seeks to regulate and monitor the design, testing and evaluation, manufacture, packaging, labelling, import, sale, usage and

disposal of medical devices, to ensure the availability of safe medical devices for human use in the country. Article 66 describes the essential principles in this legislation: the use of medical devices should not compromise people's health and safety; their design and manufacture must conform to safety principles; they should be suitable for the intended purpose; their long-term safety must be assured; they should not be adversely affected by transport or storage; and their benefits must outweigh any side effects. All of these are desirable objectives.

The bill was required because the current medical devices regulations have become "non tariff" barriers in international trade. Hence the promotion and growth of medical devices industry in the country requires effective and prudent regulation incorporating the current accepted principles of Global Harmonizing Task Force.

Despite its deficiencies, Srinivasan said, the bill is an improvement on the existing framework in which there is nothing specific on regulation of devices. However, this bill does not provide for the same level of safeguards as are put in place for drug research. It has some broad essential principles which, if brought into practice, will create an impetus for clinical evaluation of medical devices. The regulatory authority could list disqualified or blacklisted clinical investigators, producers and manufacturers, as is followed by the USFDA under its application integrity policy. (It is alarming that one can find a large number of Indian names and titles in that list.)

A look at the categorisation of devices undertaken by the USFDA gives an indication of the range of items to which the regulation must relate – from breast pumps, contact lenses, tanning devices and wrinkle fillers to breast implants, heart valves, balloon catheters, defibrillators, tourniquets, catheters, haemodialysis, oxygen regulators.

Srinivasan concluded with the suggestion that a minimum agenda should be set for device regulation: rationality, evidence-based policies and actions, honesty and transparency, coupled with quick action on those violating ethical norms.

Building the framework to regulate research within an unregulated healthcare system

The final speaker in the panel, **Abhay Shukla,** spoke on the overall scenario of the regulation of healthcare services. Ethical problems in clinical trials represent a microcosm of the problems that afflict the health system as a whole. The issue therefore is not about correcting specific aberrations but about bringing order to a mostly private and largely unregulated healthcare system.

When there is no comprehensive mechanism to ensure patients' rights, the rights of trial participants are likely to be violated, Shukla pointed out. Moreover, unethical practice is a characteristic of the larger healthcare system – a highly privatised system based on out-of-pocket spending in which a large proportion of people lacks access to healthcare and may be induced participate in clinical trials. At present, 80% of outpatient care and 60% of inpatient care in the country is provided by the private medical sector, and the public sector is marginalised. This situation calls for a larger, systemic regulation.

The overall healthcare regulatory scenario is grim. Most states do not have any regulatory mechanism. Though a few states like West Bengal, Delhi, Andhra Pradesh and Maharashtra have some regulatory mechanism, much of it is focused on registration of clinical establishments and, at most, on insistence on physical standards. There is no precise information even about the number of private clinical establishments at a national level, let alone the different types, covering different systems of medicine, and at the national as well as state levels.

The National Health Policy, 2002, "envisages the enactment of suitable legislation for regulating minimum infrastructure and quality standards in clinical establishments/medical institutions by 2003." However, no such legislation has been enacted as of 2009. The draft bill for the National Public Health Act was sent to a parliamentary standing committee and suggestions elicited and incorporated. But it has not been presented in the legislature for approval. Clearly the process of regulation of healthcare establishments is very slow. This is despite the fact that the union government has launched major initiatives such as the National Rural Health Mission and the Urban Health Mission to revitalise the health sector.

The National Health Policy and the National Public Health Bill lack a clear framework of principles or any core standards of regulation. The bill also lacks any reference to patients' rights. There is no requirement for enquiry prior to registration; the onus of verification and complaint regarding standards is put on the general public. There is no participatory mechanism to monitor implementation. The bill also does not make any mention of public health obligations or emergency medical care by private establishments. Civil society organisations are not represented in the entire framework. In other words, the bill merely focuses on the formality of registration and pays lip service to the concept of regulation to monitor standards of care and promote patients' rights.

The experience in different states has been varied. In Maharashtra a comprehensive set of rules was drafted for the Bombay Nursing Home Registration Act, 1949, through a broad consultative and collective process involving health rights groups, private practitioners, academics and the government. But these are yet to be enacted. They were submitted to the health department which made some modifications. The draft was uploaded on the ministry website in July 2006. However, the rules are yet to be operationalised. It is imperative for all those in the health movement in Maharashtra to ask questions about the non-implementation of the modified Act and Rules.

One key component of the BNHRA rules drafted by this collective is the standard charter of patients' rights, the result of inputs from various stakeholders. It mentions the right to different kinds of information, to privacy and dignity, to informed consent before any invasive or high risk procedures, treatment or the initiation of any research. Establishments undertaking clinical research are required to have documented policies and procedures to guide all research activities in compliance with national (ICMR) and international guidelines.

The enactment of such rules, if they are accepted and implemented, will be a step forward. However, the history of regulation in India consists of such good pieces of draft legislation, which is approved by a part of the public health system but remains to be enacted and operationalised.

Summarising the key issues related to the regulation of healthcare services, Shukla stated that there has been a historical dichotomy between the

public and the private sector which needs to be resolved. Standards, and patients' rights, must be uniform across the public and private sectors. They should based on universal principles and not the paying or non paying status of users. It has often been proposed that self-regulation through a process of accreditation should take the place of a law. However, both the law and self-regulation are necessary and not substitutable. A voluntary process of accreditation does not absolve the state of its responsibility to regulate healthcare services. Often, initiatives to introduce regulation are equated with increased bureaucratisation and met with suspicion or contempt. However, a process of *social regulation* is needed, which involves civil society and users' representatives as well as providers of healthcare services in both the public and the private sector.

Till date, regulation has not moved beyond physical standards. There is a need to develop rigorous standards for processes as also to define and codify patients' rights in order to have a comprehensive regulatory framework.

Operationalising the regulation of healthcare institutions

Several issues need to be resolved before regulation can be considered. One relates to reconciling the needs and capacities of medical institutions in the inequitable system that exists in India. For example, the requirement for a blood bank within a specified distance of a hospital has different implications for urban and rural areas; it could deprive rural areas of access to hospital facilities altogether.

Another issue is of bringing the different systems of medicine under one regulatory framework. The phenomenon of cross practice (when those trained in one system of medicine practise another system) needs to be addressed within such a framework. There is a dearth of information for the formulation of guidelines or standards, particularly in the area of rational therapeutics.

There has been little discussion on the regulation of financial aspects of healthcare services through setting charges and ceilings for services and professional fees based on rational standards. This is necessary to protect patients from exploitation. It is often remarked that private insurance companies will bring about regulation of services in order to reduce costs. However, regulation through the market mechanism using private

insurance as the medium cannot provide a comprehensive solution to the regulation issue. This requires a commitment to a universal access healthcare system, based on principles of patients' rights.

Standards of care should be streamlined and integrated across the public and private sectors. There are many schemes for social insurance covering specific sections of the working class, such as the Employee State Insurance Scheme and the Central Government Health Scheme. These should be merged and extended. A large section of the working class is in the unorganised sector and deprived of any social security. A social security network, that includes health insurance, should be developed for the informal sector. In order to increase the availability of and access to services for the vulnerable, there needs to be a substantial expansion of the public sector provisioning of services. Moreover, the state has provided substantial benefits to charitable trusts which have set up hospital services but failed to fulfil their obligations to provide free care. The mandated "free beds" in these hospitals should be brought under public management as a step towards socialising healthcare services. Simultaneously, consensus needs to be reached on rational care and reasonable costs. This is critical for maintaining quality and equitable access to healthcare services.

Eventually, one hopes for a socialised system of healthcare that integrates state managed services with regulated private services at the primary, secondary and tertiary care levels. This would be funded by state revenue generated through taxation and social insurance mechanisms for both the organised and unorganised sectors. The regulatory framework would be based on participatory principles with the involvement of all stakeholders, bolstered by community-based monitoring of healthcare delivery.

A lack of political will is the most important barrier to this socialised system of healthcare. This political will must take on the powerful medical lobby which is hostile to regulation. Users are weak, unorganised, vulnerable and largely ineffective in countering the medical lobby. This is combined with a myopic ruling class that has not effectively acted against the medical lobby. To counter the paralysing effect of this deadlock, we require a broad-based socio-political coalition that includes progressive sections of the medical fraternity and committed political representatives. This coalition should initially press for the first level of regulation based on standards and patients' rights. This would build the base for the second level of transformation towards a socialised system of healthcare, to provide universal access, and be buttressed by larger socio-political processes across multiple sectors.

Conclusion

The discussion at the seminar made it clear that an environment of good governance and sound regulatory mechanisms alone can sustain regulation of clinical research. The emphasis in recent times on ethics and regulation in research is divorced from other aspects of the healthcare sector such as the oversight mechanisms themselves, drug manufacturing and the healthcare services. It is not possible to regulate research without an overall framework of good governance. Contradictory trends have also emerged: the government has taken some measures to improve regulation of research and simultaneously stalled the process of instituting effective regulations in healthcare services and in allied sectors such as the production of drugs and devices.

Research participants are rendered more vulnerable because of the inequitable distribution of healthcare resources. Poor patients are often induced to participate in trials in order to obtain treatment. Patients in public sector hospitals are unable to question actions of the providers because they are availing of free services and do not have the resources to get alternative services.

The concept of equity is closely related to that of good governance of healthcare services. In India, there are several mechanisms through which the state subsidises the private sector or finances it – giving land to build infrastructure, offering tax and customs duty exemptions or through public-private partnerships. In all such arrangements, the private sector is supposed to provide free services to the poor. These obligations are not fulfilled: hospitals falsify their records to fabricate lists of patients treated "free"; or they register patients as "free patients" but accept payments in the form of donations. In public-private partnerships, private providers charge patients fees even when they receive reimbursements from the government for treating them.

At the same time, public sector provisioning of healthcare services has stagnated or even declined. The poor are thus effectively excluded from both sectors. Access to free drugs is currently restricted largely to disease

control programmes such as for tuberculosis, malaria and HIV/AIDS. The poor have almost no access to free drugs for chronic diseases. Moreover, with the exception of some disease control programmes, free drugs may be obtained only if one avails of services from the public sector. Thus, for most conditions, a majority of the population purchases drugs from the market. The cost of medicines often constitutes the major expense in the household health budget. This burden is aggravated due to irrational and unethical medical practice and the prescription of formulations with questionable therapeutic value. Providers' prescription practices are influenced by the promotional strategies of drug companies. Thus, drug production, pricing and distribution must be regulated in order to ensure the availability of affordable, safe, effective and appropriate drugs.

Finally, the sites of healthcare practice – health facilities – are themselves poorly regulated. There is no universal provision for registering facilities, monitoring services and grievance redress. Unlike other universal access systems, today patients' entitlements in health facilities differ according to the type of facility – public or private. There is a piecemeal provision of rights rather than a comprehensive framework of rights guaranteeing healthcare. While protection from malpractice and negligence may extend to users of all kinds of services, private institutions can legally withhold services from those unable to pay. Moreover, there is almost an exclusive dependence on the market mechanism to weed out substandard services. This ignores the fact that healthcare providers, not patients, make decisions on healthcare, and they can obtain monopolistic control over practice.

The monitoring of quality within the public sector, though more organised and systematic, is often hampered by a lack of resources and availability of personnel, both for the delivery of services as well as for the monitoring function itself.

In particular, public accountability is missing in most existing regulatory mechanisms. Some attempts have been made to introduce community-based monitoring systems. However, these cannot be effective without ensuring the deployment of adequate personnel and finances for implementation. without being linked to funding decisions and personnel management. Community-based monitoring remains, at best, a local

advocacy strategy which enables people to articulate their demands and become more aware of their rights. It does not fulfil the critical function of devolving power to the users.

The seminar provided an important opportunity for outlining areas of ethical concern in clinical research against the broader context of an inequitable, overburdened and diverse healthcare system. It reflected on the options available to all those concerned about ethics and equity – whether researchers, manufacturers, administrators or activists – to come together and contend with the challenges posed by the inevitable growth of commercial clinical research in India.

Annexures

Clinical Trials and Healthcare Regulation in India

: Seminar programme :
Introduction to the K R Memorial Lecture Series: **Padma Prakash** Introduction of participants
: Session 1 : **Investigating the conduct of international clinical trials in India**
Chairperson: **Sanjay Nagral** The context of clinical research in India: **Amar Jesani** 'Their bodies our drugs' Clinical trials in low income countries for European market authorisation: **Annelies den Boer** Investigation of three clinical trials, main findings: **Sandhya Srinivasan / Sachin Nikarge** Discussants' remarks and chairperson's remarks Discussants: **Urmila Thatte, Soumitra Pathare** Open discussion
13.15 to 14.00 LUNCH
: Session 2 : **Legal and ethical issues in the regulation of healthcare**
Chairperson: **George Thomas** Panel discussion Panelists: **Mala Ramanathan:** Role of IECs in the regulation of clinical trials in India **S Srinivasan:** Legal and ethical issues in the regulation of drug and device production **Abhay Shukla:** Social regulation of healthcare services, the scenario and the options Open discussion and summing up by the chairperson

Introduction to the speakers

Padma Prakash is a trustee of Anusandhan Trust and **associated with** *esocialsciences.*

Amar Jesani is managing trustee of Anusandhan Trust. He is also a member of the editorial board of the *Indian Journal of Medical Ethics*.

Annelies den Boer is project coordinator, medicines, WEMOS, Netherlands.

Sanjay Nagral is former chairperson Forum for Medical Ethics Society and consultant surgeon.

Sandhya Srinivasan is executive editor, *Indian Journal of Medical Ethics* and a freelance journalist.

Soumitra Pathare is a consultant psychiatrist and associated with the Centre for Mental Health Law, Indian Law Society, Pune.

Urmilla Thatte is head of the department of clinical pharmacology, KEM Hospital, Mumbai, and a member of a number of ethics review committees.

George Thomas is an orthopaedic surgeon and editor, *Indian Journal of Medical Ethics*

Mala Ramanathan is faculty at the Achutha Menon Centre for Health Sciences Studies, Thiruvananthapuran.

S Srinivasan (Chinu) is **managing trustee** of LOCOST (Low Cost Standard Therapeutics), Vadodara, a non profit trust involved in drug manufacturing

Abhay Shukla is coordinator of SATHI - CEHAT, a centre of Anusandhan Trust.