Q & A on Clinical Trials and the HPV Case

The Indian Supreme Court will hear the arguments concerning a petition on human rights violations in a clinical trial. In this case, ECCHR submitted an Amicus Brief to the Court on 11th of February 2014. 24,000 girls in Gujarat and Andhra Pradesh had been vaccinated against the human papilloma virus (HPV), which causes most cervical cancer cases. After news reports about irregularities, a parliamentary inquiry committee concluded that the trial was conducted without proper informed consent or monitoring. It especially questioned the fact that school head masters signed consent forms on behalf of the children. Women's health activists now seek accountability and brought a public interest petition to the Court.

Overview Questions:

The HPV Proceedings before the Indian Supreme Court

What is public interest litigation?
Who are the petitioners?
Who are the respondents?
Which human rights were violated?
What do the petitioners demand?
Are the vaccinated girls involved in the lawsuit?
Why is the case before the Supreme Court?
What is an Amicus Curiae Brief?
How were women particularly affected by these violations?

The HPV Vaccination Project

Which companies manufactured the vaccines?
Which organization was responsible for the implementation of the clinical trial?
What did the Indian Enquiry Committee do?

Clinical Trials

What is outsourcing?
What is offshoring?
What is a clinical trial?
Can it still be a clinical trial if the product is already on the market?
What are the different phases of clinical trials?
What are adverse events?
Are there differences between informed consent in normal medical interventions and informed consent in relation to clinical trials?

The New Legislation on Clinical Trials in India

Which impact did the PIL petition have on the regulation of clinical trials in India?
How was the legal framework reformed? (How was the regulation on informed consent improved?)
What happened to other on-going clinical trials?
How have corporations reacted to these changes?

The HPV Proceedings before the Indian Supreme Court

What is public interest litigation?

Public interest litigation (PIL) was developed by the Indian Supreme Court in the late 1970s. It allows members of the public to file a petition on behalf of others who are not able to approach the court. It aims to "bring justice within the reach of the poor masses, who constitute the low visibility area of the Humanity" as the Court put it in one of its cases (Indian Supreme Court P.U.D.R vs UOI, in AIR 1982 SC 1473).

In its guidelines the court indicates that it will accept the following issues as a PIL petition: bonded labour, neglected children, petitions from prisoners, petitions against the police, atrocities on women, children, scheduled casts and tribes, environmental matters, and "other matters of public importance." The litigation does not need to be adversarial in nature, in terms of one party seeking relief against another. It is rather intended to vindicate the public interest by demanding that violations of constitutional and legal rights of a large number of people will be noticed and redressed. A PIL can be filed by any "public spirited" citizen.

Who are the petitioners?

Petitioner 1: Kalpana Mehta, founder member of Saheli Women's Resource Centre. For 30 years she has been active in the women's health movement. She worked on campaigns against hazardous contraceptives and for a womencentric approach to contraception. For the past 14 years she has been with the organization Manasi Swasthya Sansthan in Indore to provide quality health care to economically disadvantaged women.

Petitioner 2: Nalini Bhanot, Voluntary Health Association of India in the area of public health. She has authored 'Taking Sides' a book on primary health care issues and has worked on child rights and various other initiatives relating to PDS, an acute Iodine deficiency.

Petitioner 3: V Rukmini Rao, Gramya Resource Centre for Women. Its vision is to create a just society, which will provide political, social and economic opportunities for women. They especially focus on tribal and dalit women, to help them achieve their rights, improve their lives and livelihoods and realize their full potential. They work closely with Community Based Organizations, women's organizations, youth leadership, and like-minded Civil Society Organizations to seek justice for marginalized communities.

Which human rights were violated?

1. The right to informed consent

Valid informed consent requires the following elements: voluntarism, information disclosure and decision-making capacity. According to Article 7 of the International Covenant on Civil and Political Rights (ICCPR) medical experimentation without informed consent is considered "*torture or cruel, inhuman or degrading treatment or punishment*". Moreover "[*i*]*n particular, no one shall be subjected without his free consent to medical or scientific experimentation*."

2. The right to health

Article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) recognizes the right of everyone to enjoy the highest attainable standard of physical and mental health. A lack of monitoring during a clinical trial constitutes also a violation of this right to health, since monitoring is essential to identify injuries and respond promptly and adequately. Article 12.2(d) ICESCR requires States to take step towards the "*creation of conditions which would assure to all medical services and medical attention in the event of sickness*." The creation of these conditions is hindered if a proper monitoring system is not set up.

3. The right to special care

In this case the trial subjects were entitled to special care. This right is entailed in three different international human rights covenants.

- The Convention on the Right of the Child (CRC). Article 24 (1) affirms the rights of the child to the enjoyment of the highest attainable standard of health.
- The Convention on the Elimination of All Form of Racial Discrimination (CERD). Article 5e (iv) obliges the States to guarantee the right of everyone in the enjoyment of the right to public health and medical care.
- The Convention to Eliminate All forms of Discrimination Against Women (CEDAW). Article 12(1) obliges the States to take "*all appropriate measures to eliminate discrimination against women in the field of health care in order to ensure (..) access to health care services*."

<u>Which laws are violated according to the petitioners?</u>

According to the petitioners, the HPV vaccination project may have violated the Constitution of India. In particular, article 21's protection to life and personal liberty, as well as articles 14 and 15 which provide for the right to equality and non-discrimination. The petitioners also allege violations of the International Convention on Economic, Social, and Cultural Rights (ICESCR) and the Convention for the Elimination of all forms of Discrimination Against Women (CEDAW), namely the right to the highest attainable standard of physical and mental health and to ensure that girls give informed consent and have access to adequate health care.

The inadequate informed consent process is further suggested to violate Indian regulations, because Schedule Y of the Drugs and Cosmetics Rules states:

> "…All pediatric participants should be informed to the fullest extent possible about the study in a language and in terms they are able to understand. Where appropriate, pediatric participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written consent form..." (para. 161 of the petition).

The petitioners also argue that the ICMR guidelines for biomedical research were not adhered to, even though they deal in detail with the informed consent process (para. 193 of the petition):

> "For all biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed consent protects the individual's freedom of choice and respect for individual's autonomy and is given voluntarily to participate in research or not.

> Adequate information about the research is given in a simple and easily understandable unambiguous language in a document known as the Informed Consent Form with Participant/ Patient Information Sheet."

Who are the respondents?

There are nine respondents mentioned in the petition: the Union of India, the Drugs Controller General of India (DCGI), the Indian Council of Medical Research (ICMR), the States of Andhra Pradesh and Gujarat, PATH International, the manufacturers MSD Pharmaceuticals Pvt. Ltd. and GlaxoSmithKline Pharmaceuticals Asia Pvt. Ltd., and Christian Medical College. The Court has so far only asked the Union of India, the DCGI, and PATH for replies.

What do the petitioners demand?

A particular feature of public interest litigation is that the court can, for example, order government agencies to conduct certain investigations, provide guidelines for future action, or provide certain information. Thus, the petitioners demand:

- Access to information about the clinical trial and HPV vaccines in India, specifically information from PATH, the states of Andhra Pradesh & Gujarat, and the DCGI
- Order the Christian Medical College to do a fact-finding mission regarding the current health of those administered the vaccines
- Order to determine culpability of the CRO and the state governments
- Order to start criminal investigation
- Provide guidelines regarding civil and criminal liability for clinical trials in India

Are the vaccinated girls involved in the lawsuit?

It is not easy to trace the girls that were vaccinated. There were fact-finding missions to the state of Gujarat and the state of Andhra Pradesh. These led to interviews with some of the vaccinated girls or their families.

Why is the case before the Supreme Court?

Public interest litigation petitions are immediately filed to the Supreme Court if the facts concern more than one state.

What is an amicus brief?

An amicus brief presents relevant information to the court not already brought to its attention by the parties and aims to assist the judges in deciding the case. It literary means „Brief from friends of the Court", through which valuable information about legal arguments can be provided. It can help, for example, to shed light on how a case might affect people other than the parties to the case, and to show which effects a certain decision could have on them.

The HPV vaccination project

Which companies manufactured the vaccines?

The vaccines were distributed by MSD Pharmaceuticals Pvt. Ltd., the Indian subsidiary of the pharmaceutical company Merck headquartered in the United States, and GlaxoSmithKline Pharmaceuticals Asia Pvt. Ltd., the Indian subsidiary of GlaxoSmithKline, headquartered in the United Kingdom.

Which organization was responsible for the implementation of the clinical trial?

The project was designed and executed by PATH (Program for Appropriate Technology in Health), a US based NGO in collaboration with the Indian Council for Medical Research (ICMR) and the State Governments of Andhra Pradesh and Gujarat.

What did the Enquiry Committee do?

The Enquiry Committee received the background information on the HPV vaccination project from the ICMR, such as the protocols, copies of approvals, and notes of meetings of advisory committees. After deliberation, the committee identified further documents it would need and received further documents from PATH, GSK, and Merck, including, for example, serious adverse events reports and samples of consent forms. The Committee further invited the principle investigator from PATH, the district immunization officers and the Chairman of the Ethics Committee to a meeting. Three medical experts were asked to assess the information that was obtained and their briefs are incorporated in the final report of the Committee.

On clinical trials

What is outsourcing?

Outsourcing means that pharmaceutical companies let another organization conduct their clinical trials. These organizations are called 'contract research organizations.' During the past decade this practice has become more common. According to some estimates, there are about 1,100 companies operating in this business.

What is off-shoring?

Off-shoring means that pharmaceutical companies move their clinical trials outside of their home country, currently most frequently to Brazil, China, India, or Eastern Europe and increasingly also to South Africa and Kenya.

What is a clinical trial?

According to the US Food and Drug Administration, a clinical trial is a research study in human volunteers to answer specific health questions. The Indian Schedule Y in the Drugs and Cosmetics Rules defines "Clinical trial" as "*…a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and or efficacy of the new drug*" (Schedule Y Rule 122DAA, Drug and Cosmetic Rules).

Can it still be a clinical trial if the product is already on the market?

The ECCHR Amicus Brief has been written on the assumption that the vaccination project was a clinical trial and should have adhered to the corresponding guidelines. According to the Final Report of the Enquiry Committee appointed by the Government of India, PATH has argued that the HPV vaccination program was only a "demonstration project" which should not have to fulfill the requirements for clinical trials (even though PATH sought approval for a clinical trial and an effort was made to ensure consent) (Final Report of the Committee appointed by the Govt. of India, February 15, 2011). The Enquiry Committee, however, concluded that "*by whatever name you call it, the project proposal has been carried out as research on human participants. And as such it had to follow all the guidelines and statutory requirement applicable for research on human participants" (*Report Enquiry Committee 2011 under 7.1.3).

What are the different phases of clinical trials?

Generally, there are four phases of clinical trials. Phase 1 is about risk management and is done with healthy volunteers. Phase 2 is about the therapeutic effect. Phase 3 aims to confirm the therapeutic effect, and Phase 4 is conducted after marketing approval and is about the use and safety surveillance.

What are adverse events?

It might be instructive to note the terminological difference between „adverse event" and „adverse reaction" (or "adverse effect"), whereas a reaction does not necessarily have a causal

relationship with the treatment, an effect must be a response to the investigational medicinal product (this distinction is made in the EU Directive 2001, Article 2 (m) and (n)).

Are there differences between informed consent in normal medical interventions and informed consent in relation to clinical trials?

The doctrine of informed consent, which receives widespread recognition and use in the context of medical treatment, is of equal if not greater significance within the context of drug experimentation. Medical practitioners abide by a code of moral conduct that requires them to operate in the best interests of the patient similar to a fiduciary, researchers follow a different set of professional norms. They undertake research projects for the furtherance of scientific knowledge. Clinical trials can only be examined for their adherence to a scientifically and ethically sound protocol, which outlines the risk-benefit justification for participating in the study.

The new legislation on clinical trials in India

Which impact did the PIL petition have on the regulation of clinical trials in India?

On 3 January, 2013 the Indian Supreme Court admitted the PIL filed on 6th February 2012 by Swasthya Adhikar Manch, Indore & others. With this PIL the petitioners prayed for "… *an order directing the establishment of a Committee of Experts consisting of members of civil society (..) to examine the present legal provisions concerning clinical trials (..) and to make recommendations to this Court regarding guidelines that are necessary to be followed in clinical trials*".

Accepting the PIL, the Court pointed out the negligence of the Ministry of Health and Family Welfare and the Central Drugs Standard Control Organization (CDSCO) in addressing the issue and asked them to act urgently. Moreover the Court ordered to set up a special panel for the submission of an affidavit to shed light on any irregularities in the drug trials.

Further actions have been prompted by the Supreme Court in order to address the concerns around clinical trials: (1) there was a reform of the existing legal framework; (2) several trials were suspended; (3) the regulation on informed consent was improved.

How was the legal framework reformed?

Following requirements of the court the Government passed on 30th January 2013 certain amendments to the Schedule Y of the Drug and Cosmetics Rules, which aim to tighten the norms on the condition of clinical trials.

The rights of the trial subjects are aimed to be strengthened. In particular:

- The right of the trial subject to free medical management in case of an "adverse event";
- The right of the trial subject and his/her nominee(s) to financial compensation in case of an "adverse effect";

Further duties for subjects who aim to carry out clinical trials have been formalized. In particular:

- The duty of the Sponsor to undertake the provision of medical management and the compensation in these cases;
- The duty of the Investigator to provide to the trial subject, through informed consent process, information about essentials of the trial and his/her rights;
- The duty of the Investigator to report to competent institutions about any kind of "serious adverse events" happening during the trial.

What happened to other on-going clinical trials?

On 31 August, 2013 a parliamentary panel (the Standing Committee) submitted a report alleging irregularities committed during the conduct of studies on the HVP vaccine as well as lapses in monitoring the trial procedures by the India´s Drug Controller General (DCGI). As a consequence of those findings the Supreme Court ordered on 30 September, 2013 the suspension of the approval procedures by the DCGI of 162 new chemical entities until

efficient monitoring mechanisms will be introduced. With a further order passed on 21 October, 2013 it also suggested to the DCGI to set up monitoring standards.

How was the regulation on informed consent improved?

On 19 November, 2013 India´s Ministry of Health and Family Issues cleared that the trial subject's consent has to be given after receiving understandable, non-technical oral and written information. Moreover it ordered, in pursuance of the Supreme Court´s orders, that visual and audio recording of the informed consent processes has to be done and the documentation shall be preserved adhering to the principles of confidentiality.

On 9 January, 2014 the CDSCO (Central Drugs Standard Control Organization) published a draft of the "Guidelines on audio – visual recording of informed consent process in clinical trial." The document sets out the aforementioned requirements aiming to provide guidelines for all of the stakeholders involved. Information has to be given to the trial subject on:

- the purpose of the research,
- the expected duration of the participation,
- the reasonably foreseeable risks,
- the expected benefits,
- the description of medical management and financial compensation in case of injury or death and the explanation about whom to contact for trial related queries and the right of the subject to withdraw at any time.

Any restriction of these rights will undermine the validity of the consent. The guidance also requires that oral consent must be obtained through recording procedures.

How have corporations reacted to these changes in the Indian legislation?

As a consequence of the reforms and of the suspension of several drugs approvals, some companies are considering shifting their clinical trials to other countries. Many pharmaceutical sponsors criticized the unpredictability of schedules and uncertainty in the result of the procedures.

It has been argued that the process is going to take much longer than expected and the costs would increase up to ten or twenty-fold. This might lead to changes in the policies of the companies which have until now conducted low-cost clinical trials in India.

Furthermore, the provisions on compensation in case of adverse events have led some Canadian and US institutes to suspend several ongoing clinical trials in India. Several companies consider moving their trials to Europe and US. Others have already set up trial phases in Malaysia and Thailand. It is moreover suggested by commentators that some sponsors may prefer to carry out their trials in China, South Korea and Russia which provide a comparatively flexible and less strict regulatory atmosphere.