

VACCINE CLINICAL TRIAL IN CHILDREN IN LOW- AND MIDDLE- INCOME COUNTRIES

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Key International Clinical Trial Standards

- **Declaration of Helsinki**
 - Developed by World Medical Association in 1964 and amended thereafter.
 - Not legally binding, but adopted by almost all countries.
- **ICH E6: Guideline for Good Clinical Practice**
 - The Regulatory Members of ICH are expected to implement the guidelines as their commitment to become a Regulatory Member of ICH.
- **ICH E11- E11A: Clinical Trials in Pediatric Population**
 - The 2000 version was adopted by EC, Japan MHLW/PDMA, Health Canada, US FDA and Swissmedic.

Regulatory Environment in Low- and Middle- Income Countries

- **History**

- Governments may be unclear as to whether a therapy being offered in a time of epidemic or crisis is experimental or proven
- Core research norms such as informed consent of the individual may be not properly established or difficult to implement
- Local resources for providing oversight are often weak

- **Regulations and Policies are Changing**

- Work with international institutions to update the regulatory system
- Regulations on trial subject protection and safety continues to be improve

India

Laws and Regulations on Clinical Trials

- The Drug and Cosmetics Rules, 1945 (DCA, 1940/DCR, 1945)
- Schedule Y: Drugs and Cosmetics (11th Amendment) Rules, 2005—
Notification
- IN-GCP: Good Clinical Practices for Clinical Research in India
- Ethical Guidelines of the Indian Council of Medical Research

Note: Significant changes to the laws and regulations have been made since 2013.

Nigeria

Laws and Regulations on Clinical Trials

- Nigerian Code of Health Research Ethics (2007):
- NAFDAC Good Clinical Practice Guidelines 2016
- Documentation Guidelines for Clinical Trial in Nigeria

Ethical Issues in Clinical Trials in Nigeria

Abdullahi v. Pfizer, Inc., 562 F.3d 163 (2d Cir. 2009)

Background

Study:

In 1996, Pfizer carried out a clinical trial of its new antibiotic drug Trovan on children in Nigeria's infectious disease hospitals to obtain US FDA's approval of the new drug for children. Pfizer failed to secure the proper informed consent of either the children or their guardians.

Trovan:

- To treat bacterial meningitis.
- In 1998, the FDA approved for use on adult patients only. It was eventually restricted to adult emergency care only after reports of liver failure emerged.
- In 1999, the EU banned Trovan.

Ethical Issues in Clinical Trials in Low- and Middle Income Countries

Abdullahi v. Pfizer, Inc., 562 F.3d 163 (2d Cir. 2009)

Decision:

-The prohibition on non-consensual medical experimentation on humans is a customary international law norm.

Cases After Abdullahi

-*Abdullahi* is precedent in US courts.

-[*Estate of Alvarez v. Johns Hopkins Univ.*](#), 205 F. Supp. 3d 681 (2016)

- From 1946 to the early or mid-1950s, officials of the United States Public Health Service engaged in unethical medical experimentation in Guatemala and concealed their actions for some sixty years.

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

Background:

- **Study Name:** A Post-licensure observational study of HPV vaccination: Demonstration Project
- **Start:** in 2007
- **Sponsors:** PATH in collaboration with the respective State Governments and the Indian Council of Medical Research in the relevant districts
- **Location:** Districts of Khammam, Andhra Pradesh and Vadodra, Gujarat
- **Objective of the Study:** generating evidence that would enable policy makers to decide on possible public sector introduction of the HPV vaccine
- **Other information:** The HPV vaccine for the project had been donated by the manufacturers, viz. GSK and MSD to PATH.

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

- In 2010, local newspaper reported the deaths of seven girls who had received HPV vaccine under the project.
- Due to concern of the public, the study was suspended and an enquiry Committee was constituted by the Government to look into the alleged irregularities in the conduct of studies.
- The Committee issued its final report on the “Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine” by PATH in India in 2011
- The Parliamentary Standing Committee on Health and Family Welfare issued its report on the study in 2013.
- Kalpana Mehta and Other Petitioner(s) v. Union of India and Others Respondent(s) was filed with the Supreme Court of India in 2012.

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

2011 Final Report

- Issues required to be enquired by the Committee:
 - Link between the deaths and vaccination
 - Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate consent

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

The process of consent taking:

2011 Final Report

“Government of Andhra Pradesh, Tribal Welfare Department had issued a circular for vaccination in various schools instructing all the hostel welfare offices ...to sign the consent forms on behalf of adolescent girls to have vaccine....This was done because contacting parent was difficult in the agency area.”

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

2013 Parliamentary Report

- unlike the assertion from PATH that the project was not a “clinical trial”, the project had to follow all the guidelines and statutory requirements applicable for research on human participants;
- the project was troubling, such as the choice of countries and population groups, the monopolistic nature, at the point of time, of the product being pushed, the unlimited market potential and opportunities in the universal immunization programs;
- ICMR’s decision to support “the use of the HPV vaccine” before the vaccine was approved in India and to promote inclusion in the Universal Immunization Program before any independent study was questionable

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

2013 Parliamentary Report

- a very large number of parents/guardians were illiterate and could not even sign their local language i.e. Telugu or Gujarati (in the case of Gujarat, 6,217 forms were signed, 3,944 had thumb impressions;
- the ethics committee didn't play the role they were designed;
- the use of the NTHM logo for the project implemented by a private, foreign agency as well as the identification of this project with the UIP has adversely affected and damaged the credibility of the programme;
- the actions taken by the DCGI is not adequate to fix the problem and avoid future violations, and etc.

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

Kalpana Mehta Litigation

Kalpana Mehta and Others Petitioner(s) v. Union of India and Others Respondent(s)

- Filed in 2012, and is still in process
- Respondents:
 - Union of India and ORS. Ministry of Health and Family Welfare Secretary;
 - Central Drugs Standard Control Organization Drug Controller General;
 - ICMR Director General;
 - the State of Andhra Pradesh Directorate of Health Services Principal Secretary;
 - The State of Gujarat Public Health and Family Welfare Department Principal Secretary;
 - PATH International Director;
 - Glaxosmithkline Asia PVT. LTD. CEO;
 - MSD Pharmaceutical PVT. LTD. CEO;
 - Christian Medical College Director;
 - The State of Telangana Chief Secretary.

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

India HPV Vaccine Study Scandal

Kalpana Mehta Litigation

- The Supreme Court of India's order dated 12 August 2014 posed seven questions to the government, including
 - Were proper procedures followed?
 - What actions has the Government taken since the 2013 Parliamentary report?
 - Why were Gujarat and Andhra Pradesh chosen?
 - What caused the deaths and disabilities?
 - What follow-up is ongoing?
 - Was informed consent obtained?
 - What kind of protocol for observation must be in place?

Ethical Issues in Vaccine Clinical Trials in Low- and Middle Income Countries

Thank you.

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