

Chapter 5

Cervical Cancer Screening in India

Sandhya Srinivasan, Veena Johari and Amar Jesani

Abstract Three clinical trials took place in India between 1998 and 2015 in urban and rural areas of Mumbai, Osmanabad and Dindigul. The trials aimed to determine whether trained health care workers could conduct cervical cancer screening in a community using cheap methods of testing – primarily visual inspection with acetic acid – to reduce the incidence and mortality rate of cervical cancer. The clinical trials were conducted on approximately 374,000 women, of whom about 141,000 were placed in the control arm (no screening). Although the standard of care for testing of the disease in India has been cytology screening (or Pap smear) since the 1970s, screening for cervical cancer was not available universally under a government programme, and for the study purposes the standard of care was therefore misconstrued to be no screening. Known and effective methods of screening for cervical cancer were therefore withheld from 141,000 women in areas where it was known to be of high incidence and prevalence. This placed them at a known risk of developing invasive cervical cancer, and dying from it, because it was not detected and treated in time. Two hundred and fifty-four women in the no-screening arm died due to cervical cancer as per the latest published reports on the three trials. A no-screening control arm would not have been allowed in the USA, but was accepted by the US funders for clinical trials in India. It is imperative that ethical standards for research be applied equally across nations to prevent “ethics dumping” and protect the rights of human research participants in research, no matter where they are located on the globe.

Keywords Clinical trials · India · Cervical cancer · Women · Standard of care

The date periods for deaths in the no-screening arms are taken from the dates quoted in the last available publication on each trial. They are: 98 in Mumbai 1998–2011 (Shastri et al. 2014), 64 in Osmanabad 2000–2007 (Sankaranarayanan et al. 2009), 92 in Dindigul 2000–2006 (Sankaranarayanan et al. 2007). The Mumbai trial reported findings up to 2011, though the trial would not have ended before 2015.

S. Srinivasan (✉) · V. Johari · A. Jesani
Indian Journal of Medical Ethics, 8 Seadoll, 54 Chimbai Rd, Bandra West, Mumbai 400 050,
India
e-mail: sandhya_srinivasan@vsnl.com

Area of Risk of Exploitation

While the trials described in this case study showed a number of ethical shortcomings, the main area of risk of exploitation was a placebo arm – no screening for cervical cancer despite high incidence and prevalence – instead of provision of an accepted standard of care.

Context

Medical and public health research had crossed national boundaries during colonial times; but controversies on ethical violations in research conducted by those from high-income countries (HICs) in low- and middle-income countries (LMICs) became a real focus once higher ethical standards were established in the HICs. LMICs however have continued to lag far behind in bringing such standards into their legal and ethical systems.

This unevenness in ethical and legal standards has been used by HICs to carry out research at reduced financial costs in LMICs. Many participants in such research have suffered avoidable injuries and deaths. The international bioethics debate has chastised researchers from HICs for practicing “double standards” (Macklin 2004), taking advantage of vulnerable people in vulnerable nations and thus “exploiting” them for their own scientific goals and profit motives. Inequities among researchers, and in ethics standards, have since become major issues of concern in international collaborative research.

The globalization of neoliberal economic policies has pressured LMICs to open their markets and deregulate their economies. The establishment of the World Trade Organization in 1995 created an international trade regime favourable to HICs. One major issue in international trade is the “dumping” of cheap and/or substandard commodities by powerful nations into the economies of less powerful nations, with a devastating negative impact on their economies (Howell and Ballantine 1998).

“Ethics dumping” follows the same pattern as dumping in trade, but in slightly different ways. Ethics dumping takes place because doing such research is either not possible at all in the HIC concerned or entails high costs due to the value attached to the ethical standards it is required to follow. This is matched in the low- or middle-income country (LMIC) by either a lack of adequate ethical standards in its guidelines or a failure to convert such guidelines into law and mandatory requirements and enforce them. At the same time, the suffering of many people from a range of communicable and non-communicable diseases may render such research relevant to the LMIC, and may also tempt local scientists to undertake it with inadequate ethical standards, in order to find well-intentioned solutions.

While research of this kind may or may not provide an early solution to a medical problem suffered by people, the need for a solution invariably tends to provide a justification for using a lower ethical standard, according less importance

to respect for participants, or to the avoidable injuries and deaths of vulnerable subjects. Overall however, it causes irreparable harm to the nation's desire to bring ethical standards up to an international level.

We provide an example of ethics dumping in three trials conducted from 1998 to 2015 in urban and rural India on testing for cervical cancer. These were funded by the USA's National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation (BMGF), a private foundation that supports public-private partnerships in the development of technological solutions and their inclusion in government programmes, in collaboration with the International Agency for Research on Cancer (IARC) in France, a specialized cancer agency of the World Health Organization (WHO).

These trials have been condemned as unethical by public health experts and ethicists because the participants were not offered the same level of protection and consideration as participants in HICs would have been. Women in the no-screening arm of the three trials were merely observed to determine how many would get cervical cancer and how many would die, if they were never screened. Issues relating to informed consent, the use of placebo or control arms of the trial (in this case no screening) despite awareness of and the in-principle availability of well-known effective methods of testing for cervical cancer (e.g. Pap smear), a lack of proper supervision in the intervention arm of the trial, and irreversible harm to the women participants have marred these trials and resulted in human rights violations.

Background on Cervical Cancer Screening in India

Cervical cancer is the fourth most common cancer in women worldwide, with 85% of the global burden of disease in LMICs (Ferlay et al. 2013). It is a leading cause of cancer mortality in Indian women over the age of 15, and too often women die because they do not get prompt diagnosis and treatment. Researchers note:

Nearly 70% of cervix cancer patients in India present at stages III and IV. Around 20% of women who develop cervix cancer die within the first year of diagnosis and the 5-year survival rate is 50% (Mittra et al. 2010).

This cancer affects poor women the most, especially those living in rural areas, because they are less likely to get screened and treated, and therefore more likely to develop invasive cancer and die from it (Krishnan et al. 2013).

In HICs, regular screening programmes for the early detection of precancerous lesions, and their prompt treatment before they progress to invasive cancer, have led to a reduction in incidence of and deaths from cervical cancer (Sankaranarayanan et al. 2001). The international standard of screening is cytology, or the Pap smear, an examination of cells on the surface of the cervix for precancerous lesions. Another test involves the DNA of the human papillomavirus (HPV), a viral infection closely associated with the development of cervical cancer. The HPV test,

which is manufactured by various companies, is being advocated for routine use in HICs, where it costs substantially more than cytology.

Cytology screening has been used in Indian public health services since the 1970s and is available in all major hospitals in the country. Since at least 2001 it has been advocated for inclusion in the government's cancer control programme services (Sankaranarayanan et al. 2001). In 2006, guidelines developed by the Indian government and WHO advocated the use of the Pap smear at district level, along with a cheaper, simpler screening method at the primary health centre level (National Cancer Control Programme 2006). The HPV test is available in the private sector in India, but it is very expensive. Though cytology is available all over India, researchers have held that it is not feasible for population screening in a country like India:

Cervical cancer prevention researchers and advocates have argued that the standard approach in high-income countries, namely cytology-based screening, is difficult to establish in LMICs where laboratory infrastructure; trained personnel, such as cyto-technicians and pathologists; and continuous quality assurance processes are largely unavailable ... Consequently, research has focused on evaluating screening approaches requiring less training and fewer clinic visits and using existing (or minimal additional) human resources (Krishnan et al. 2013).

An inexpensive cervical screening method is visual inspection of the cervix to detect precancerous lesions. Since at least the 1990s, studies have been conducted of various visual inspection methods, with or without magnification, and after application of contrast chemicals such as acetic acid or iodine to highlight precancerous lesions. These methods do not need to be conducted by a medical professional. By 1999, visual inspection of the cervix after application with acetic acid (VIA) was considered a "promising approach in the detection of cervical neoplasia" (Sankaranarayanan et al. 2003) for cancer prevention programmes. VIA was being advocated for inclusion in the cancer screening programme as early as 2001, but it was felt that definitive information on the value of VIA was still lacking.

Study Design

The value of a screening intervention as a public health measure is judged by various criteria: sensitivity, specificity and positive predictive value of the test; the feasibility of implementing it in a health programme, its cost-effectiveness, and its impact on incidence and mortality. Such information is gathered through various types of research, including cross-sectional studies, mathematical modelling, implementation projects and cluster randomized controlled trials (CRCTs).

Within the scientific community, the CRCT is a classic trial design to evaluate an intervention in the community. The CRCT provides the gold standard of evidence necessary for making public policy decisions. CRCTs test an intervention (preventive or therapeutic) for a disease or condition by giving it to a "cluster" of people, and comparing the results to a control group of clusters, who are given

another intervention. The clusters can be slums within a municipal ward, or villages covered by a single primary health centre. The group or sample is chosen from a larger community using a system of randomization that is meant to eliminate all differences between the two groups (e.g. age or parity) other than the intervention being studied.

When there is no existing effective intervention for the disease being studied, then a trial may compare the intervention to a placebo (e.g. a “dummy pill”). When a non-drug trial tests a preventive intervention such as screening, then the “placebo” arm is a “no-screening” arm. However, ethical guidelines governing the use of placebo in research severely restrict the use of placebo or “no intervention” *if an effective treatment or test already exists for the disease being studied*. This is to ensure that research participants in the control arm do not receive a lower standard of care than is already known to be effective, and are not therefore disadvantaged by their participation in the study. This had been asserted in a number of national and international documents published prior to and during the three trials undertaken in this case study (WMA 2008; ICMR 2000, 2006; CIOMS 2002). The World Medical Association’s *Declaration of Helsinki* first introduced strict guidelines on the use of a placebo control in 2000 (WMA 2000).

Three Cluster Randomized Controlled Trials of VIA with “No Screening” Controls in India

In a review of cervical cancer screening in LMICs, R. Sankaranarayanan et al. described research on cervical cancer screening in India, which included studies of the impact of awareness and health education, and cross-sectional studies of various visual inspection-based approaches as well as HPV testing. They concluded by mentioning three studies:

There are three large, ongoing cluster-randomized intervention trials in India – in Dindigul district (Tamil Nadu), in Mumbai, and in Osmanabad district (Maharashtra) – to evaluate the effectiveness of VIA in reducing cervical cancer incidence and mortality. The intervention programme in Osmanabad district aims to address the comparative efficacy and cost-effectiveness of three different primary screening approaches in reducing the incidence and mortality: VIA, conventional cervical cytology, and HPV testing. The results of these studies are likely to provide valuable leads to the development of public health policies to control cervical cancer in developing countries (Sankaranarayanan et al. 2001).

The trials were conducted on a total of 374,000 women. The 141,000 women in the control arms of these trials received no screening for cervical cancer, but were provided with the so-called “usual care” or “standard care”, consisting of health education on cervical cancer symptoms, screening and treatment, and the availability of these facilities in their localities. According to the last published report on each trial (Sankaranarayanan et al. 2007, 2009; Shastri et al. 2014), a total of 548

women were recorded to have died in the trials, 254 of them in the no-screening control arms.¹

The use of no-screening control arms went against all established ethical principles, as articulated in national and international guidelines: namely, that new interventions must be tested against a proven effective method. In the case of the VIA trials, cytology screening was a proven effective method, and it was available in health services all over the country, including in the institutions which conducted these trials.

When a controversy about these trials using a no-screening control broke out, one of the investigators stated: “Whenever a new intervention is evaluated, it is compared with the standard of care existing in the country”. In India, he wrote, there “is no organised or large-scale opportunistic cervical cancer screening programme” anywhere in the country. As a result, “[t]he standard of care for cervical cancer control in India is clinical diagnosis and treatment of invasive cancer only when symptomatic women seek medical attention” (Sankaranarayanan et al. 2011). Another researcher stated: “Pap smear cannot be considered the standard of care in India, not only because of the lack of infrastructure and trained manpower, but also because it is not cost-effective” (Pramesh et al. 2013).

All the women recruited in these trials were poor and socially disadvantaged, and thus highly vulnerable. The Mumbai study was conducted on women in slum clusters living in tenements, shanties on open ground, or makeshift huts on the pavements and along the railway lines. Osmanabad, Maharashtra, is “a predominantly rural and socio-economically backward district with a high incidence of cervical cancer” (Sankaranarayanan et al. 2005). Between 25–30% women lived in thatched roof houses. Dindigul, Tamil Nadu, is a rural district whose high incidence of cervical cancer was a reason to choose it as the site of this VIA trial. Some 65–75% of the women in Osmanabad and Dindigul and 40% in Mumbai had no formal education. The average age of the women in these trials was 40–45 years (range 30–59). They would have had poor access to health care, whether because of cost or the inconvenience of long waiting lines and ill-equipped public services or the low priority given to self-care. Though it is known that the vast majority of women, particularly after they have given birth, suffer from various gynaecological symptoms, 90% of women in the Mumbai trial had never visited a gynaecologist with their complaints.

The Mumbai Trial

The first study to start was in Mumbai, at the Tata Memorial Hospital and Centre (TMC), a national centre of excellence for cancer research and policy. The study,

¹The figures are based on the start and cut-off dates given in the study reports: Dindigul: 2000–2006, Osmanabad: 2000–2007, Mumbai 1998–2011. The Mumbai trial concluded in 2015, but reported results as of 2011.

entitled “Early detection of common cancers in women in India”, was funded by the US National Institutes of Health. The study initially sought to find out if repeated rounds of screening using inexpensive techniques would reduce mortality from cervical cancer.

Women community health workers educated up to the tenth grade were trained to conduct screening with VIA and also to do clinical breast examination for the detection of breast cancer. They were required to be supervised, and about 10% of women screened were also to be tested by the researchers for cross-checking of the results. Women in both arms were given health education on the causes of cancer. They were also told about the need for screening, and that the screening and treatment were available. Then the women in intervention/experimental arms were given screenings for cervical cancer, while women in the control arms were given no screening at all.

The trial started in 1998 and concluded in December 2015. A total of 75,000 women in the intervention arm and 76,000 women in the no-screening arm were recruited into this trial. Each woman was in the trial for 17 years. *Women in the intervention arm* were given health education and screening four times, i.e. once every two years. Those who tested positive were directed to TMC, where they were given confirmatory tests and treatment if needed. After the four rounds of screening were over, the women were then contacted four times, once every two years, for follow-up. *Women in the control arm*, on the other hand, received health education only once, were not offered any preventive screening for carcinoma cervix, and were observed through surveillance for 17 years. Every two years, through active surveillance, data of women in the control arm were collected to find out the number that developed cervical cancer or died as a result of it. In 17 years, seven rounds of active surveillance were carried out in both arms to document the development of cervical cancer and deaths due to it.

Changes were made to the study protocol over a period of time. The intervention was initially “direct visual inspection” without any magnification or contrast, a technique that had been judged obsolete before this trial began, and was later changed to VIA. The sample size increased from about 35,000 in each arm initially to about 75,000 in each arm. The objectives were later amended to include reduction in the incidence of cancers. These details do not appear in the published reports of the study. Cross-checking of test results by the researchers was also performed for fewer than 10% women in the intervention arm.

In 2011, an American physician filed a complaint with the US government’s Office of Human Research Protections (OHRP), relating to the Mumbai and Osmanabad trials. An application for documents was also filed by a journalist under the US Freedom of Information Act. The OHRP stated that its jurisdiction was limited to trials funded by the US government and did not apply to research funded by the Bill and Melinda Gates Foundation (BMGF), a private party (Suba 2014).

The OHRP’s investigation found irregularities in the functioning of TMC’s institutional review board: standard operating procedures had not been followed, meeting minutes were not documented, and decisions were taken without a quorum. The OHRP also found discrepancies in the informed consent document between the

English and the local language translation (Marathi). The English form gave information on cervical cancer, the tests required for its detection and where testing was available, but the Marathi form did not.

The OHRP did not find the no-screening arm of the trial to be unethical. By 2011, 98 women who had entered the control arm of the Mumbai trial and received no screening, only health education, had died of cervical cancer. The results of the Mumbai trial were announced at the 2013 meeting of the American Society of Clinical Oncology. The researchers announced that a test for cervical cancer, using just vinegar and conducted by trained health workers, could bring mortality from cervical cancer down by 31% (ASCO Post 2013). The findings were reported extensively in the press.

Osmanabad Trial

In October 1999, TMC with its Rural Extension Project and the Nargis Dutt Memorial Cancer Hospital started a second trial, in the Osmanabad district in rural Maharashtra. They were funded in this trial by BMGF.

This trial compared the impact of a single screening of VIA, HPV test or cytology to a no-screening control arm in a CRCT. The primary outcomes were the incidence of cervical cancer and the associated rates of death. The researchers stated in their interim report:

Whether a screening program using VIA or HPV testing will be followed by a reduction in disease burden and the cost-effectiveness of these alternate approaches based on real program-based information remain to be established. These approaches need to be evaluated in comparison with the established standard cytological screening, with respect to their comparative efficacy and cost-effectiveness, before recommendations can be made concerning their introduction in a public health context (Sankaranarayanan et al. 2005).

Women in the intervention arm were identified through household surveys, and those who consented to be in the trial were given information on cervical cancer and its prevention, and invited to screening camps in each village where trained midwives conducted the screening. Depending on which intervention arm the village belonged in, the women received VIA, Pap smear or the DNA test for HPV. Women with positive VIA tests were given immediate follow-up tests and on-the-spot treatment if appropriate; or they were referred to the Nargis Dutt Hospital for further treatment. Samples from the cervix were taken from women in the cytology and HPV arms, and the results sent to them in two weeks. Those with positive tests were given appointments at the hospital for follow-up. Women in the control arm were given education on cancer and its prevention and information about the services available at the Nargis Dutt Hospital. “Since there is little screening for cervical cancer in India, women who did not undergo screening (control group) were considered to receive the standard of care” (Sankaranarayanan et al. 2009).

All the women were contacted just once, at the time of the intervention, after which they were surveyed and tracked through the cancer registries and death registries, until the end of the eight-year follow-up period. The trial was conducted in partnership with the IARC and the Association for Cervical Cancer Prevention (ACCP). The ACCP is a member of the IARC and both receive some funding from the BMGF. Screening was started in January 2000 and completed by April 2003 (Sankaranarayanan et al. 2005). The findings of the interim report of the Osmanabad trial ran contrary to standard wisdom:

Our results show that a high level of participation and good-quality cytology can be achieved in low-resource settings. VIA is a useful alternative but requires careful monitoring. Detection rates obtained by HPV testing were similar to cytology, despite higher investments (Sankaranarayanan et al. 2005).

However, when the final findings were reported in 2009, the researchers concluded that while a single round of screening for HPV reduced both incidence and mortality from cervical cancer, cytology and VIA were no better than no screening at all. The researchers observed that while the test used in the trial, by Digene Corporation, was effective, a cheaper HPV test had been developed, manufactured by Qiagen, a Chinese company.

Our results, combined with those of the Chinese study of the new HPV test, indicate that HPV testing is appropriate as a primary screening approach in low-resource settings for women who are at least 30 years of age (Sankaranarayanan et al. 2009).

These comments gain significance when one learns that in 2004, Digene had entered into a partnership with the Program for Appropriate Technologies in Health (PATH), an implementing agency for BMGF, to promote the use of HPV testing in LMICs. In 2007, Qiagen Corporation bought Digene Corporation.

Dindigul Trial

The third trial started a few months after the Osmanabad trial. In May 2000, BMGF with IARC initiated another trial of VIA, this one with the Christian Fellowship Community Health Centre hospital in Ambilikkai, Dindigul District, Tamil Nadu. The objective was to evaluate the efficacy of a single round of VIA provided by nurses, with appropriate treatment approaches, in reducing the incidence of and mortality from cervical cancer.

The women in the intervention arm were screened with VIA by trained nurses. Those found positive were offered cryotherapy on the spot, and those with larger lesions were referred for treatment. Screening was completed by April 2003. The control group received “existing care”. “No active intervention was provided for the control group” (Sankaranarayanan et al. 2004). The researchers explained: “We used an unscreened control group because there are no organised screening programmes in India” (Sankaranarayanan 2007).

Information on incidence and mortality was collected from cancer and mortality registries as well as through active follow-up. Follow-up started in September 2003 and was to continue until 2012. However, by December 2006 the researchers concluded that a single round of VIA followed by appropriate treatment reduced incidence and mortality significantly. “Timely implementation of an affordable and effective screening strategy in developing countries is thus crucial, while waiting for further improvements in HPV testing, vaccine technology, costs, and its widespread use” (Sankaranarayanan 2007).

Analysis

While ethics and human rights often offer universal frameworks for research, their actual implementation differs from country to country. Basic ethical principles of research such as those of informed consent, cautions on research on vulnerable populations and the need for monitoring mechanisms to protect participants are laid out in international guidelines. The three trials described in this case study are evidence that principles of research ethics are not always translated into practice.

The VIA trials demonstrate ethics dumping, and the harm that it causes to participants in host LMICs. These trials would never have been granted ethical approval in the USA or France, the countries of the sponsors and collaborator. They exploited local regulatory weaknesses and economic and social inequities. They were pushed, approved and accepted by the sponsors (NIH and BMGF in the USA) and collaborator (IARC in France) to be conducted in India on poor and vulnerable women.

In these three trials, rights of the women participants in the no-screening control arm were violated: the universal and fundamental right to life and the right of access to the highest available standard of care. It was known that as poor women, they were already at increased risk of developing cervical cancer, and denying them known effective and potentially lifesaving screening put them at a predictable risk of developing invasive cervical cancer and dying from it. The denial of screening delayed not only the detection of the disease, but also access to appropriate and timely treatment that could have saved their lives. The standard of care was wrongly construed by the researchers as meaning the universal availability of tests under a programme of the government in India, rather than the universal standard of care used for testing of the disease, which was available in India.

For the purpose of public health policy, there was no need for a natural history control arm with no screening. The researchers should have provided an active control arm using one of the known methods of testing for cervical cancer, as they would have had to if the trials had been conducted in the USA or France.

In addition, the trials ignored the importance of informed consent. Women in the trials were not given adequate information. This violated their right to life, vitiated their consent and rendered the trial highly unethical. A trial without the participants’ voluntary and informed consent would not have been permitted in an HIC.

What made these unethical trials possible? What were the conditions that enabled ethics dumping in the VIA trials? One needs to understand why host countries seek international support for research, why sponsors fund this research, and whether these reasons are justifiable. These reasons may include: a shortage of locally available funds for research; the interest of organizations in HICs in conducting research in LMICs as part of their international health agendas; and the relationships between local institutions and international organizations, as well as researchers' own links with these organizations as part of their individual scientific careers. All these create a web of relations that lies at the heart of the resulting double standard.

Research ethics must also contend with the view (Prasad et al. 2016) that locally relevant research justifies lower ethical standards. The researchers in these studies have argued that these studies are important because cervical cancer affects and kills poor women in LMICs more than it does women in HICs, and this calls for a test that is inexpensive, implementable and effective. They have also asserted that double standards do not cause active harm, as there is no functional screening system in the host country.

Finally, the women participants in both experimental and control arms of these trials are poor, voiceless and invisible. They may view participation in such trials as giving them access to some care. When faced with a powerful medical establishment, they are reluctant to make their grievances public. For instance, the hospital conducting the Osmanabad trial is the only such service in the area. In such a situation, violations of research ethics are less likely to come into the public eye.

Ethical Implications of Research in Communities Without Universal Access to Health Care

Researchers in the VIA trials did not provide the standard of care to participants in the control arm, arguing that India did not have an effective universal screening programme and its standard of care for cervical cancer prevention was therefore “no care”.

Most LMICs, barring a few honourable exceptions, do not have *universal* access to health care. Even when the government is supposed to provide free access to health care, individuals are frequently forced to seek care in the private sector and pay for it. The care that people receive is therefore determined not by a universal standard but by what they can afford, or what the government provides, and many people do not get any care whatsoever. This situation has permitted researchers to interpret the standard of care, and their own responsibilities as physician-researchers, in a way that is not in the best interests of research participants.

The standard of care *cannot* depend on, or be defined according to, whether or not it is universally accessible. In the VIA trials, the Pap smear is the universal standard of care because it is universally considered to be an effective screening test for cervical cancer. Any woman who goes to a private or public hospital should

expect to be offered it. It is part of the Indian government's cancer prevention programme.

Whether or not the community involved in research has universal access to the standard of care, through the government or private or social insurance, researchers and sponsors must be held responsible for providing this standard preventive, diagnostic and curative care free of cost to participants in the control arm of a trial. There is therefore a need to have an explicit provision in ethics guidelines and in the law emphasizing researchers' ethical obligation to provide standard care to participants in the control arm, as they are under their direct care during the course of research.

Regulatory Weaknesses

Guidance for ethics review of non-drug trials is included in the ethical guidelines of the Indian Council of Medical Research (ICMR) for biomedical research on human participants (ICMR 2006). The ICMR guidelines acknowledge that the denial of available treatment to a control group is unethical. They also state that "proper justification should be provided for using the placebo" and that "[i]n keeping with the Declaration of Helsinki *as far as possible standard therapy should be used in the control arm*" (ICMR 2006) (emphasis added).

However, since the trials were non-drug related, prior permission from the Drugs Controller General of India was not required. Thus the VIA trials did not have any legal oversight. The regulatory roles were played by institutional committees – the institutional ethics committees, scientific review committees and data safety monitoring committees. In this case, their authority was limited to within the institution and they were not accountable to a regulatory authority.

US regulatory bodies claimed inability to investigate and act on complaints of unethical research in the Osmanabad and Dindigul trials as these were funded by a private foundation. Hence, these trials were not accountable to the US regulator as they were not government-funded. Private foundations in HICs fund a substantial amount of collaborative research in low-income countries, and their lack of accountability to any authority is a matter of concern.

In the case of the Mumbai trial, the US regulatory body applied double standards. The use of a retrospective waiver of written informed consent, or permission to obtain consent after the intervention, goes against the very principle of prior informed consent in research, and would not have been allowed in the US. Likewise, the US OHRP did not conclude that the no-screening arm in the Mumbai trial was ethical, although it would not have been possible in the US. The trial even continued when the relevant local hospital ethics committee in Mumbai stated that the use of a no-screening arm was unethical.

Information about the actual trials, apart from the published papers, was not readily available. This prolonged the harm done to the participants, as it delayed the response to claims about the unethical and illegal nature of the trials.

Recommendations

The following steps are necessary to prevent ethics dumping between HICs and LMICs.

- ***Ensure the regulation of collaborative research.*** Studies involving international collaboration should only be allowed in LMICs if mechanisms are in place which ensure that the rights of participants will be respected at all times, and that sponsors, researchers, ethics committees or institutions, whether governmental or private, operating both inside and from outside the host country, are held accountable for their activities in the LMIC.
- ***Ensure a framework for transparency.*** Mechanisms must be put in place to ensure that trials are conducted in an open and transparent manner, and information about ongoing trials must be available and open to expert scrutiny, so as to prevent harm at any stage of the trial. The anonymized data, findings and conclusions of the researchers should be open to scrutiny, so that the findings and decisions on whether they should be used in public health policy can be properly evaluated.
- ***Provide compensation for research-related injury.*** Mariner (1997) writes:

Since most legitimate research is intended to benefit society as a whole, the subject assumes risk for society's sake (some would say making a gift to society). Therefore, society has a moral obligation to make the injured subject whole by compensating those who took the risks and suffered thereby. In addition, it may be argued that where society conducts, supports, or sponsors research, it voluntarily assumes an obligation to compensate those who are injured in its enterprise.

Sponsors and researchers must compensate participants who suffer from trial-related injuries, by offering diagnostics and treatment freely and by providing monetary compensation for loss, injury, harm, mental and physical suffering, and expenses incurred as a result of participating in the trial. The mechanism should be simple, so that it causes minimal problems to the participants. In the above trials, proper follow-up of the women in the control arms, testing them with the best known methods, and providing treatment and compensation would be a step in the right direction. Families of women who died due to the standard of care being withheld, thereby preventing them from accessing timely treatment, must also be compensated.

References

- ASCO Post (2013) ASCO 2013: Cervical cancer screening using visual inspection with vinegar reduces mortality by 31% in large study in India. The ASCO Post, 6 June. <http://www.ascopost.com/News/4202>
- CIOMS (2002) International ethical guidelines for biomedical research involving human subjects. Council for International Organisations in Medical Sciences, Geneva

- Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2013) GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012 v1.0. IARC CancerBase No. 11. International Agency for Research on Cancer, Lyon. <http://globocan.iarc.fr>
- Howell TR, Ballantine D (1998) Dumping: still a problem in international trade. In: Wessner CW (ed) International friction and cooperation in high-technology development and trade: papers and proceedings. National Academy Press, Washington CD, p 325–377
- ICMR (2000) Ethical guidelines for biomedical research on human participants. Indian Council of Medical Research, New Delhi. <http://web.archive.org/web/20010613180317/http://icmr.nic.in/ethical.pdf>
- ICMR (2006) Ethical guidelines for biomedical research on human participants. Indian Council of Medical Research, New Delhi. http://www.icmr.nic.in/ethical_guidelines.pdf
- Krishnan S, Madsen E, Porterfield D, Varghese B (2013) Advancing cervical cancer prevention in India: insights from research and programs. Health, nutrition and population discussion paper. World Bank, Washington DC
- Macklin R (2004) Double standards in medical research in developing countries. Cambridge University Press, Cambridge
- Mariner W (1997) Compensation for research injuries. In: Mastroianni AC, Faden R, Federman D (eds) Women and health research: ethical and legal issues of including women in clinical studies, vol 2: workshop and commissioned papers. Institute of Medicine and National Academy Press, Washington DC, p 113–126
- Mitra I, Mishra GA, Singh S, Aranke S, Notani P, Badwe R, Miller AB, Daniel EE, Gupta S, Uplap P, Thakur MH, Ramani S, Kerkar R, Ganesh B, Shastri SS (2010) A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *International Journal of Cancer* 126(4):976–984. doi:10.1002/ijc.24840
- National Cancer Control Programme (2006) Guidelines for cervical cancer screening programme: recommendations of the expert group meeting. Government of India – World Health Organization Collaborative Programme (2004–2005). Department of Cytology & Gynaecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. http://screening.iarc.fr/doc/WHO_India_CCSP_guidelines_2005.pdf
- Pramesh CS, Shastri S, Mitra I, Badwe R (2013) Ethics of “standard care” in randomised trials of screening for cervical cancer should not ignore scientific evidence and ground realities. *Indian Journal of Medical Ethics* 10(4):250–251
- Prasad V, Kumar H, Mailankody S (2016) Ethics of clinical trials in low-resource settings: lessons from recent trials in cancer medicine. *Journal of Global Oncology* 2(1): 1–3
- Sankaranarayanan R, Budukh AM, Rajkumar R (2001) Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ* 79 (10):954–962
- Sankaranarayanan R, Esmey PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, Fayette JM, Cherian J (2007) Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 370(9585):398–406
- Sankaranarayanan R, Nene BM, Dinshaw K, Rajkumar R, Shastri S, Wesley R, Basu P, Sharma R, Thara S, Budukh A, Parkin DM (2003) Early detection of cervical cancer with visual inspection methods: a summary of completed and on-going studies in India. *Salud Pública de México* 45 (suppl. 3):S399–S407
- Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, Malvi SG, Chinoy R, Kelkar R, Budukh AM, Keskar V, Rajeshwarker R, Muwonge R, Kane S, Parkin DM, Chauhan MK, Desai S, Fontaniere B, Frappart L, Kothari A, Lucas E, Panse N (2005) A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *International Journal of Cancer* 116(4):617–623

- Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA (2009) HPV screening for cervical cancer in rural India. *New England Journal of Medicine* 360(14):1385–1394
- Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Malvi SG (2011) Reply to S D Rathod's Commentary on HPV screening for cervical cancer in rural India. *Indian Journal of Medical Ethics* 8(3):182–183
- Sankaranarayanan R, Rajkumar R, Rajapandian T, Pulikattil OE, Mahe C, Bagyalakshmi K, Thara S, Frappart L, Lucas E, Muwonge R, Shanthakumari S, Jeevan D, Subbarao TM, Parkin DM, Cherian J (2004) Initial results from a randomized trial of cervical visual screening in rural south India. *International Journal of Cancer* 109:461–467
- Shastri SS, Mitra I, Mishra GA, Gupta S, Dikshit R, Singh S, Badwe RA (2014) Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *Journal of the National Cancer Institute* 106(3):dju009. doi:10.1093/jnci/dju009
- Suba EJ (2014) US-funded measurements of cervical cancer death rates in India: scientific and ethical concerns. *Indian Journal of Medical Ethics* 11(3):167–175
- WMA (2000) WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. World Medical Association. [http://www.who.int/bulletin/archives/79\(4\)373.pdf](http://www.who.int/bulletin/archives/79(4)373.pdf)
- WMA (2008) WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. World Medical Association. <http://ethics.iit.edu/ecodes/node/4618>

Author Biographies

Sandhya Srinivasan is a Mumbai-based freelance journalist and researcher. She was executive editor of the *Indian Journal of Medical Ethics* from 1998 to 2011 and is now consulting editor. She is also consulting editor for scroll.in, a digital daily of political and cultural news in India, and a trustee of the Centre for Communication and Development Studies, a non-profit organization advocating for social justice and sustainable development in India.

Veena Johari is a Mumbai-based lawyer working on human rights and public health. She was with the Lawyers' Collective HIV/AIDS Unit before setting up Courtyard Attorneys, which focuses on access to medicines and opposition to patents on pharmaceutical drugs. She is the legal expert in the research ethics committee of the King Edward Memorial Hospital in Mumbai, and is on the editorial board of the *Indian Journal of Medical Ethics*.

Amar Jesani is an independent consultant, researcher and teacher in bioethics and public health. He is co-founder of the Forum for Medical Ethics and current editor of the *Indian Journal of Medical Ethics*. He is visiting professor at the Centre for Ethics at Yenepoya University, Mangalore, and associate faculty at the Centre of Biomedical Ethics and Culture, Karachi. He is a member of the Institutional Review Board at the Tata Institute of Social Sciences, Mumbai, the International Research Ethics Committee of Médecins Sans Frontières, and the Central Ethics Committee of the Indian Council of Medical Research.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

