Ethics of 'standard care' in randomised controlled trials of screening for cervical cancer

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Cervical cancer is the second most common cause of cancer-related death worldwide and kills over 70,000 Indian women every year (1). Early detection of abnormalities in cervical cells before they progress to cancer, and appropriate treatment, can save many lives. The research priority in developing countries is effective screening tests and treatment programmes that can be run with limited resources and training (2).

The main screening method under research in developing countries is visual inspection of the cervix after staining it with acetic acid (VIA). Another is the Pap smear, or cytology-based screening (2). VIA and the Pap smear pick up most, but not all, abnormalities that might progress to cancer. The Pap smear is the gold standard of screening, but needs trained personnel and more resources. VIA is simpler and cheaper, and has also been used as a 'first screening test' with positive cases tested with a Pap smear. A third, more expensive, test is for infection with the Human Papilloma Virus (HPV) as this virus is known to lead to cervical cancer. All screening must be followed by confirmatory tests and treatment.

In June 2013, researchers at Tata Memorial Centre, Mumbai, presented the results of a trial evaluating VIA. The researchers calculated that VIA screening followed by treatment could prevent 22,000 cervical cancer deaths in India annually (3).

This trial is one of three cluster randomised controlled trials on cheap screening and treatment for cervical cancer, in rural and urban India (2), conducted with government and international support, to examine interventions for introduction into the public health programme.

Two of these trials are being investigated for unethical trial designs and practices (4). The third, also testing VIA, seems to have escaped scrutiny though its trial design is the same: testing the efficacy of an intervention by not providing the control group effective and available care. Essentially these trials used a placebo as a control when a treatment existed.

The use of a placebo or 'no treatment' control

These studies received ethics review and approval around the time of the campaign against placebo controlled trials on treatments to prevent mother-to-child transmission of HIV (5). The placebo control controversy led to amendments in the Declaration of Helsinki's ethical guidelines on medical research. The current version, last amended in 2008, is clear:

> *32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:*
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> - *The use of placebo, or no treatment, is acceptable 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 the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.(6). [Emphasis added]*

The guidelines of the Indian Council of Medical Research (ICMR) state:

> *In the following situations placebo can be used:*
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> *i. self limited disease;*
>
> *ii. where no proven prophylactic, diagnostic or therapeutic method exists.* (7: p 42)

The best proven screening intervention for cervical cancer is the Pap smear. There are at least three proven screening methods– the Pap smear, VIA, and testing for HPV. The women in the control arms of these trials were denied any proven intervention. As the disease for which they were screened is cervical cancer, they were subjected to risk of serious and irreversible harm.

Clearly these trials violated the Declaration of Helsinki and the ICMR guidelines.

Trials of screening for cervical cancer

The VIA trials were conducted in Mumbai slums, villages in Maharashtra and villages in Tamil Nadu, covering more than 350,000 women – 150,000 in Mumbai, 132,000 in rural Maharashtra and 71,000 in Tamil Nadu.

In the Mumbai trial, women in the intervention group were screened every two years with VIA by primary health workers and those testing positive were sent for confirmatory tests and treatment (3). In Osmanabad, rural Maharashtra. women were divided into four groups; the three intervention groups received a single examination with either VIA, or cytology-based screening, or testing for HPV, followed by confirmatory tests and treatment if needed (8). In Dindigul, rural Tamil Nadu, women were given a single round of VIA and those screening positive were given confirmatory tests and treatment if needed. Those with large lesions and invasive cancer were referred for investigations and treatment (9).

In all three trials, researchers did not provide women in the control group well established, available prevention and treatment services, on the argument that since such programmes are poorly developed in India, the 'standard' or 'usual' care against which the interventions should be compared is 'no care'. So women in the control group received only 'health education' information on cervical cancer, the importance of screening, and where it was available.

The trials actively denied care, by comparing -- as intervention and control groups -- entire clusters of urban wards or rural primary health centres, rather than individuals, ensuring that women in the control groups would not somehow gain access to the interventions.

By comparing the impact of the interventions with that of no treatment, they also violated the principle of equipoise on which such studies should be based, even though there is sufficient evidence that some screening is better than none (10).

They evaluated the intervention in terms of the incidence of and death rates from the disease, learning of the fate of the women through a review of cancer registries and government mortality data. It is not clear what happened to the women in the intervention arms of the Osmanabad and Dindigul trials who were given one-time treatment, and whether the researchers followed them up to confirm that the treatment was successful. The control arms, of course, were not monitored at all.

The treatment offered in the Osmanabad and Dindigul trials was limited to cryotherapy for small lesions. Women found to have large lesions or suspected invasive cancer were referred elsewhere for investigation and treatment. It is not known if these women had to pay for this investigation and treatment.

These studies would not have been permitted in the country of the organisations funding these trials (the US National Cancer Institute and the Bill and Melinda Gates Foundation).

These trials are only the latest examples of unethical research on cervical cancer in India, which has included monitoring women without treatment until they developed cancer (11)

Standard care

The women in the control arms in these trials received what the researchers have described as 'standard care' or 'usual care': a one-time session giving information on cervical cancer, the importance of screening, and where it was available.

'Standard care' screening for cervical cancer, in developed countries such as the US and the UK, is cytology-based, or Pap smear, screening which is acknowledged to be responsible for the marked reduction in incidence and death from cervical cancer in that part of the world (2). The test is so widely used that despite doubts about the accuracy of this test, withholding cytology-based screening as part of a study in a developed country would be considered grossly unethical.

In India, cytology-based services are offered in government as well as private hospitals. VIA is the recommended option for the district level cervical cancer control programme (2). These are the standard care in India, even if the poor quality of health services may limit women's access to them. It is grossly unethical to withhold both these available interventions from the control group in the Indian trials.

The Mumbai trial also tests an inexpensive screening method for breast cancer: health workers were also trained to conduct clinical breast examinations (CBE) for women in the experimental group. Women in the control group were educated on the value of breast cancer screening – but they were not offered a mammogram, which is the standard of care for breast cancer screening in the West. In India, it is not uniformly available, but is certainly available in the city of Mumbai where the trial took place. The researchers' explanation for not comparing CBE with mammograms is that the mammogram is a flawed test and inaccuracies in its interpretation lead to over-diagnosis and unnecessary treatment; a mammogram-based screening programme would require a large infrastructure and trained radiologists, which we cannot afford (12).

The real research questions

The researchers in these trials have argued that only a 'no care' control arm can give definitive results and this information is essential to guide policies and programmes. However, such trials do not serve the need that they claim to serve: the public health needs of resource-poor countries.

The Pap smear has been researched for decades, and VIA has been researched at least since the early 1990s. VIA is an affordable screening test, and there is evidence suggesting that it works about as well as the Pap smear. This evidence is being generated from cross-sectional studies comparing the accuracy of various screening methods; evaluations of existing public health programmes; demonstration projects to see if they are feasible and acceptable to the community; and mathematical modelling to calculate the impact of screening tests and treatment on incidence and mortality (2). Is it justified to deny trial participants proven treatment in the name of getting definitive results, given the extensive body of knowledge we already possess?

Only a fraction of women in the control groups of the three trials sought screening. Healthcare is expensive, and the poor seek care only when absolutely necessary, when illness interferes with their daily lives. Poor women are unlikely to spend time and money and negotiate an unfriendly healthcare system to get screened for a disease when they have no symptoms. In fact, by telling women about the importance of screening – and the dangers of not screening -- without ensuring them access to the necessary services may actually be more unethical than not telling them anything at all.

Maybe the focus of research should be on using the existing information in a good screening and treatment programme while addressing the barriers that women face in seeking preventive as well as curative care (1).

Regulatory failure

The VIA studies used a 'no treatment control' when both screening and treatment were available for a serious disease which if left untreated results in death – violating the principles of both national and international ethical guidelines.

Yet the proposals and, presumably, interim updates were passed by local institutional ethics committees as well as those of the funding organisations. Regulatory authories seem to have missed the obvious ethical concerns raised by these trials.

There are many other issues that deserve discussion in these and other trials looking at public health interventions in resource-poor settings. For example, should research even be conducted on less effective methods just because they are cheaper? Should a single round of screening even be tested?

This calls for an investigation into the three trials, a review of ongoing and completed research on public health interventions, and action to ensure that regulatory agencies are held accountable for monitoring such research to protect participants from harm.

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