DISCUSSIONS

Ethics of "standard care" in randomised trials of screening for cervical cancer should not ignore scientific evidence and ground realities

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We read with interest the recent editorial (1) in the *IJME* on the ethics of standard care in screening trials for cervical cancer in India. The author takes exception to the fact that three cervical cancer screening studies in India used no screening as the control arm, in spite of evidence that the Pap smear is an effective screening tool. The author argues that the Pap smear should have been the standard arm in these trials, and that it was unethical to "withhold" this screening method from participants in the control arm of the trial. At the outset, we wish to declare a conflict of interest in our response by virtue of being investigators of one of the aforesaid trials, but feel it necessary to clarify certain facts that have been overlooked. First, during the consent process, all women in the Mumbai trial (control and intervention arms) were counseled on Pap smear testing, given information on the centres nearby that offered the Pap smear and assured that they were free to get themselves screened if they so wished. Second, the author's assertion that visual inspection with acetic acid (VIA) had already been proven to be effective on the basis of cross-sectional studies, and that there was no need to perform randomised trials to prove that it was effective, lacks scientific credibility. The hierarchy of medical evidence places the randomised trial at level 1, or providing the highest level of evidence, whereas that yielded by cross-sectional studies is considered to be level 4 evidence, ie evidence that is unreliable. Major national public health policy decisions are always made on the basis of randomised level 1 evidence. Prior to our study, there had been no randomised evidence that VIA performed by trained primary health workers (who are the only healthcare providers available for the vast majority of the poor in rural and urban areas) leads to cervical cancer mortality reduction. In fact, an earlier study had shown that neither the Pap smear nor VIA had led to a decrease in mortality due to cervical cancer in India (2). Should we not obtain robust level 1 evidence before making a major public health decision to offer VIA as a routine screening method to all women in India?

Before commencing with the trial, the choice of no screening for the control arm was discussed with several experts at the national level. Three points are noteworthy. First, the Indian Council of Medical Research (ICMR) and the Ministry of Health and Family Welfare, Government of India had concluded that there was a dearth of facilities for nationwide screening for cervical cancer using the Pap smear, and had made a projection that even with a twelve-fold increase in staff trained in Pap smear, only a quarter of the eligible women in India could be screened (3). The report emphasised the urgent need for alternative methods of screening and suggested that visual examination of the cervix be evaluated (3). Second, a WHO–Government of India committee reiterated the points made in the ICMR report and, in view of the fact that the infrastructure and resources did not permit a nationwide Pap smear-based screening programme, stressed the need for the identification of an alternative method that was "scientifically correct, ethical and feasible" in India (4). Finally, a report from the Center for Risk Analysis, Department of health policy and management, Harvard School of Public Health affirmed that the Pap smear was difficult to implement in developing countries and suggested that alternative strategies be considered (5). Using mathematical modelling techniques, the report went on to compare the cost-effectiveness of the Pap smear, direct visual inspection of the cervix and human papilloma virus (HPV) DNA testing. The efficacy of once-in-a-lifetime screening with HPV DNA and direct inspection was almost identical (27% and 26% reduction in the incidence of cancer, respectively), and was superior to that of the Pap smear, which was 19%. The incremental cost-effectiveness ratio of the three techniques, when implemented three-yearly, was $460 per year of life saved (YLS) for visual inspection, while that of HPV DNA testing was 25 times higher, at $11,500 per YLS, and that of the Pap smear was even higher. The paper concluded that the Pap smear was the least effective and the most expensive amongst the techniques tested.

It becomes clear from the expert reports that the 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. The results of our study showed that VIA screening reduced the death rate from cervical cancer by 31%, ie 1 in 3 deaths were prevented. In addition, the study detected a very large number of pre-invasive cancers, which were easily treated by outpatient procedures. The latter suggests that in addition to a reduction in mortality, VIA screening promises to markedly bring down even the incidence of cervical cancer in this group in the future. Thus, the results of our study, if implemented widely, would save thousands of lives globally in the developing countries. In fact, the *Wall Street Journal*, while covering the plenary presentation of our study

(6) at the annual American Society of Clinical Oncology (ASCO) meeting, quoted experts as saying: "(VIA) … can save lives, and could even be useful in low-income areas of the US with relatively high cervical cancer rates and low use of Pap tests" (7). An international expert estimated the number of lives saved by VIA screening globally to be of the order of 270,000 per year (8).

There has always existed a healthy tension between ethics and the scientific process, but a show of moral outrage only helps to vitiate this healthy relationship.

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Screening for cervical cancer revisited: understanding implementation research

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In the editorial "Ethics of 'standard care' in randomised controlled trials of screening for cervical cancer" (1), Sandhya Srinivasan argues persuasively that a series of placebo-controlled trials on screening for cervical cancer in India were unethical. The purported aim of the trials was to study the method that uses visual inspection of the cervix following staining with acetic acid (VIA), to determine the efficacy of the method in a low-resource setting. Srinivasan notes: "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….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" (1:p149). The author also identifies the design of the research as cluster randomised trials: "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" (1:p148).

Several issues need to be sorted out to clarify what is at stake here. First, one must determine exactly what is wrong with the researchers' defence of the placebo-controlled design of the study. Second, one must identify just what type of study is needed in low-resource settings such as India. Finally, there is a need to assess the ethical acceptability of cluster randomised trials.

The researchers' defence

It is simply not true that "only a 'no care' control arm can give definitive results." Although the randomised controlled trial is the "gold standard" in clinical research methodology, this does not mean that the control arm must be a placebo. In settings in which the standard diagnostic method is a proven intervention and researchers want to test a new method, or even a less expensive method, it would be unethical to withhold the proven diagnostic method from the participants. The research design would then be a non-inferiority trial, which would test the experimental procedure against the proven intervention to see whether the former is as good (or almost as good) as the latter. That is a perfectly acceptable research design, although it would involve more research subjects and take longer than a placebo-controlled trial. The idea that it is ethically acceptable to design a study in resource-poor settings in which the participants do not have access to a proven diagnostic method outside the trial is flawed. If researchers in India wanted to study VIA to determine whether it is as good (or almost as good) as the Pap smear, they could do so in a tertiary care setting which has the equipment and trained personnel to allow for the routine use of the cytology-based screening method. Using