

in resource-poor settings" (1:p149). One critical issue is the need to distinguish clinical trials designed to study the safety and efficacy of new pharmaceutical products from those that study the implementation of interventions already proven to be efficacious in other settings. Implementation research is a useful pathway for introducing and scaling up beneficial proven public health interventions in resource-poor settings. However, it is a mistake to contend that the use of placebo controls in phase III efficacy studies of new drugs or techniques is appropriate, or even ethical, in efforts to study the implementation of proven techniques in resource-poor settings.

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## Have scientists met their ethical responsibility towards research participants?

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Pramesh and colleagues (1) have not responded to my central thesis: it was unethical to have a "no screening" control arm in the VIA trials when proven screening methods existed (2).

According to national and international research guidelines, if a proven treatment exists for the disease under study, a placebo or no treatment arm is ethically acceptable only if it is methodologically necessary (3) and the disease concerned is self-limiting, such that denying treatment will not cause serious and irreversible harm (3,4).

Given the existence and availability of Pap smear screening, as well as DNA testing for HPV, the use of a no screening arm in the trials of VIA to screen for cervical cancer violated national and international ethical guidelines for research.

1. The authors' statement regarding the information given to the participants in the Mumbai trial does not contradict anything said in the editorial; the fact that the women in the control arm were "given the freedom to get screened if they so wished" is not the same as providing them screening.
2. The authors assert: "Major national public health policy decisions are always made on the basis of randomised level 1 evidence." Decisions on public health interventions are taken using multiple sources of information. The Pap smear is one of many interventions that have been established as public health programmes in the West, and the impact measured and confirmed, without randomised trials (5). The body of research on screening methods for cervical cancer (including VIA and Pap smear) includes cross-

sectional studies, evaluation of long-standing programmes, demonstration projects, and mathematical modelling of impact and cost-effectiveness (5).

3. The authors state: "Pap smear cannot be considered the standard of care in India, not only because of lack of infrastructure and trained manpower, but also because it is not cost-effective."
  - The Pap smear is available in private and public hospitals in Mumbai, the city in which the authors carried out their research, and where the infrastructure and trained manpower necessary for its use in a screening programme exist.
  - One of the authors was also part of the Osmanabad trial (6) referred to in the editorial. This trial, the ethics of which, too, were questioned because of the use of a no screening control, was conducted through primary health centres in villages and compared VIA to the Pap smear and HPV testing. We can presume that the investigators considered all three methods to be potentially fit for use in public health programmes in rural India.
  - The authors have not explained their assertion that the standard of care is determined by cost-effectiveness, with the consequent implication that this should exclude the Pap smear from trials in India. Using the authors' argument, the Osmanabad trial should not have included the Pap smear.
  - By 2001, the ICMR had already concluded that both the Pap smear and VIA were suitable screening tests for India,

and VIA was the option recommended for immediate introduction into district cancer control programmes (5). By 2005, the WHO /Government of India committee to which the authors refer had drafted guidelines for the incorporation of both VIA (at the primary health centre level) and the Pap smear (at the district hospital level) into the existing health system, starting with a demonstration programme (7).

4. The authors state: "The choice of no screening for the control arm was discussed with several experts at the national level prior to starting the trial."

This statement does not throw any light on whether the ethics of a no screening control was discussed by these national experts, and what the conclusions were. Nor is there any mention, in the three documents cited by the authors, of a no screening control, let alone the ethics of this methodology.

Further, while ethical clearance would not have rendered the trials ethical, the authors offer no evidence to suggest that the no screening arm was even discussed by the ethics committees reviewing the trials.

5. The authors describe the editorial as a "show of moral outrage" that vitiates the "healthy tension between ethics and the scientific process." For a healthy tension between ethics and the scientific process, there must be evidence that the scientific process has considered ethics and that the scientists have met their ethical responsibility towards the research participants.

I thank Ruth Macklin for her comment (8) in support of my argument and for providing clarity to the issues raised in the editorial. Regarding my reference to the use of cluster randomisation, I did not mean to imply that all cluster

randomised trials are unethical. My intention was only to underline the consequences for the women in the control arm of these trials.

Macklin's conclusion is that the placebo-controlled VIA trials were not ethical, not necessary and not appropriate research. The question we must, therefore, ask is: why were they conducted? The response by Pramesh and colleagues does not shed any light on this question.

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## Ethical issues in adapting new technologies for rapid diagnosis

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The Xpert® MTB/RIF (hereafter Xpert) is a recent technology that has "demonstrated sensitive detection of tuberculosis (TB) and rifampicin resistance directly from untreated sputum in less than two hours" (1). Many are in favour of the widespread implementation of this technology in India. In a recent article in the *IJME*, Singh, Bhan and Upshur state that "India is ethically obliged to phase in the nationwide deployment of Xpert...as soon as reasonably possible" and "is ethically obliged to provide those diagnosed with first-line drug resistance universal access to second-line TB drugs" to treat multiple drug-resistant tuberculosis (MDR-TB) (1).

The prevalence of MDR-TB in India is estimated to be about 2%. In their review of the Xpert technology, A Trebucq and colleagues make the point that the question is not whether to treat MDR-TB, but rather, when, where and how to treat it (2). Besides the limitations related to cost (~\$10 per test), the environment required (the need for a stable, regular electric supply for an air conditioner to be able to maintain the room temperature at 15-30 °C), the shelf life of the test cartridges (18 months), and supply and maintenance issues, there are other questions as well regarding the reliability of the test at different levels of prevalence of MDR-TB. When the prevalence is 1% or less, the positive predictive value (ppv) is 32%; when the