Unethical randomised controlled trial of cervical screening in India: US Freedom of Information Act disclosures

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ABSTRACT
A randomised controlled trial conducted in Mumbai, India, compared invasive cervical cancer rates among women offered cervical screening with invasive cervical cancer rates among women offered no-screening. The US Office for Human Research Protections determined the Mumbai trial was unethical because informed consent was not obtained from trial participants. Reportedly, cervical screening in the Mumbai trial reduced invasive cervical cancer mortality rates, but not invasive cervical cancer incidence rates. Documents obtained through the US Freedom of Information Act disclose that the US National Cancer Institute funded the Mumbai trial from 1997 to 2015 to study ‘visual inspection/downstaging’ tests. However, ‘visual inspection/downstaging’ tests had been judged unsatisfactory for cancer control before the Mumbai trial began. ‘Visual inspection/downstaging’ tests failed to reduce invasive cervical cancer incidence rates in Mumbai because ‘visual inspection/downstaging’ tests, by design, failed to detect preinvasive cervical lesions. None of the 151 538 Mumbai trial participants, in either the intervention or control arms, received cervical screening tests that detected preinvasive cervical lesions. Because of missing/discrepant clinical staging data, it is uncertain whether ‘visual inspection/downstaging’ tests actually reduced invasive cervical cancer mortality rates in Mumbai. Documents obtained through the US Freedom of Information Act disclose that the US National Cancer Institute leaders avoided accountability by making false and misleading statements to US Congressional oversight staff. Our findings contradict assurances given to President Barack Obama that regulations pertaining to global health research supported by the US government adequately protect human participants from unethical treatment. US National Cancer Institute leaders should develop policies to compensate victims of unethical global health research. All surviving Mumbai trial participants should finally receive cervical screening tests that detect preinvasive cervical lesions.

INTRODUCTION
Cervical screening prevents invasive cervical cancer by detecting and treating preinvasive cervical lesions (eg, ‘high-grade squamous

Key questions

What is already known about this topic?
▸ From 1997 to 2015, the US National Cancer Institute supported a randomised controlled trial that compared cervical screening with no-screening among low-income women in Mumbai, India.
▸ The US Office for Human Research Protections determined the Mumbai trial was unethical because informed consent was not obtained from trial participants.
▸ Reportedly, cervical screening in the Mumbai trial reduced mortality rates, but not incidence rates, of invasive cervical cancer.

What are the new findings?
Documents obtained through the US Freedom of Information Act disclose that:
▸ The Mumbai trial actually studied ‘visual inspection/downstaging’ tests, which cannot detect preinvasive cervical lesions and therefore cannot reduce incidence rates of invasive cervical cancer.
▸ ‘Visual inspection/downstaging’ tests may not actually have reduced mortality rates of invasive cervical cancer in the Mumbai trial.
▸ US National Cancer Institute leaders avoided accountability for the Mumbai trial by making false and misleading statements to US Congressional oversight staff.

Recommendations for policy
▸ The US National Cancer Institute, in conjunction with other global health organisations, should develop policies to compensate victims of unethical global health research.
▸ As a first step, all surviving participants of the Mumbai trial, from the intervention and control arms, should finally receive cervical screening tests that detect preinvasive cervical lesions.
▸ Careful monitoring of detection rates for preinvasive cervical lesions is critically important to prevent the failure of cervical screening efforts in routine practice settings, irrespective of the screening technologies used.
intraepithelial lesions) before preinvasive cervical lesions progress to invasive cervical cancers. By detecting and treating preinvasive cervical lesions, cervical screening reduces incidence rates of invasive cervical cancer (ie, prevents invasive cervical cancer) and thereby also reduces mortality rates of invasive cervical cancer. A variety of screening technologies may be used to detect preinvasive cervical lesions, including Pap cytology smears, human papillomavirus tests and visual inspection with acetic acid.

From 1997 to 2015, the US National Cancer Institute funded a randomised controlled trial in Mumbai, India, that was conducted by Tata Memorial Hospital, which is the largest and most influential cancer centre in India. The Mumbai trial compared incidence and mortality rates of invasive cervical cancer among 75 360 low-income women, who were reportedly offered four rounds of visual inspection with acetic acid, to incidence and mortality rates of invasive cervical cancer among 76 178 low-income women offered no-screening. From 2000 to 2007, the Bill & Melinda Gates Foundation funded a randomised controlled trial in Dindigul District, India, that was conducted by Rengaswamy Sankaranarayanan, the Head of Cancer Screening at the WHO’s International Agency for Research on Cancer. The Dindigul trial compared incidence and mortality rates of invasive cervical cancer among 49 311 low-income women, who were offered a single round of visual inspection with acetic acid, to incidence and mortality rates of invasive cervical cancer among 50 958 low-income women offered no-screening. Concerns regarding invasive cervical cancer mortality rate measurements and unscreened control groups in randomised controlled trials of cervical screening conducted in India were previously summarised and debated with trial investigators. Important unresolved concerns remained following that debate.

For example, in 2014, the rationale offered for conducting the Mumbai trial was ‘Because Pap smear screening is not feasible in India, we need to develop effective alternatives’. However, by 2005, Sankaranarayanan, who chaired the Data Safety and Monitoring Committee for the Mumbai trial, had concluded, in the context of his controversial Osmanabad randomised controlled trial, “Our results clearly show that good-quality cytology can be implemented even in a rural setting of a developing country with reasonable investment.” The rationale for conducting the Mumbai trial was thereby invalidated by the Chair of that trial’s Data Safety and Monitoring Committee. The need to use invasive cervical cancer incidence rate and mortality rate measurements to evaluate alternatives to Pap screening also appears invalid. If, as appears likely, there were no policymakers who required these measurements, then there was no reason to collect such measurements in the first place.

In order to justify the use of unscreened control groups in the Mumbai, Dindigul and Osmanabad trials, investigators stated “we applied the principle that whenever a new intervention is evaluated, it is compared to the standard care existing in the country and only subsequently should it be implemented as a public health policy.” The principle cited by trial investigators violates Article 33 of the Declaration of Helsinki, which states “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s),” and not against the local standard. Moreover, the principle cited by trial investigators required leaders at Tata Memorial Hospital, the International Agency for Research on Cancer and the US National Cancer Institute to assume, if not to assure, that ‘no-screening’ remained ‘standard care’ throughout India from 1997 through 2015. During that time interval, between 1 million and 2 million women in India died from cervical cancer, while Pap screening became ‘standard care’ in other developing countries. Opportunity costs, borne most acutely by those most vulnerable, are associated with prioritising research on novel interventions in settings where established interventions are feasible but unavailable.

The US Freedom of Information Act is a law allowing disclosure of previously unreleased documents controlled by the US government. Herein, we report that documents obtained through the US Freedom of Information Act settle previously unresolved concerns and raise unsettling new concerns regarding the Mumbai trial. The Dindigul and Osmanabad trials were funded by the Bill & Melinda Gates Foundation, not by the US government, and are therefore not subject to oversight through the US Freedom of Information Act, or through other US government oversight mechanisms described herein.

**Prevention fails when screening detection rates are very low**

Since cervical screening reduces incidence rates and mortality rates of invasive cervical cancer by detecting and treating preinvasive cervical lesions, the most important performance measure of any cervical screening test is its detection rate for preinvasive lesions. Detection rates for preinvasive cervical lesions in India are summarised in table 1.

In 2007, the Dindigul trial reported that a single round of cervical screening using visual inspection with acetic acid had reduced incidence rates of invasive cervical cancer in Dindigul by 25%. In 2014, the Mumbai trial reported that four rounds of cervical screening, reportedly using visual inspection with acetic acid, had failed to reduce incidence rates of invasive cervical cancer in Mumbai. One intervention round prevented invasive cervical cancer (ie, reduced incidence rates of invasive cervical cancer) in Dindigul because one intervention round effectively detected preinvasive cervical lesions (table 1). Four intervention rounds failed to prevent invasive cervical cancer in Mumbai because four intervention rounds did not effectively detect preinvasive cervical lesions, as documented by the extraordinarily
Table 1 Detection rates for preinvasive cervical lesions (ie, high-grade squamous intraepithelial lesions) in India

| Study setting* | Years testing performed | Screening test studied | Numbers of women tested | Numbers of test-positive women with biopsy-confirmed preinvasive cervical lesions | Detection rates for biopsy-confirmed preinvasive cervical lesions† |
|----------------|-------------------------|------------------------|-------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------|
| Mumbai randomised trial; 2, 3 | 1998 | Visual inspection/ downstaging | 5787‡ | 18§ | 0.04% |
| First intervention round | 1998–2000 | Visual inspection with acetic acid | 45 358‡ | 8§ | 0.02% |
| Mumbai randomised trial; 2, 3 | 2000–2002 | Visual inspection with acetic acid | 41 354 ‡ | 8§ | 0.05% |
| Second intervention round | 2002–2004 | Visual inspection with acetic acid | 36 643‡ | 18§ | 0.05% |
| Mumbai randomised trial; 2, 3 | 2004–2006 (scheduled) | Not available¶ | Not available¶ | Not available¶ | Not available¶ |
| Third intervention round | 2001–2003 | Visual inspection with acetic acid | 4009** | 34** | 0.9% |
| Mumbai cross-sectional15 | 2000–2003 | Visual inspection with acetic acid | 31 343 †† | 218†† | 0.7% |

*The Mumbai randomised trial; 2, 3 the Mumbai cross-sectional study15 and the Dindigul randomised trial4 were all population-based studies.
†So that detection rates for biopsy-confirmed preinvasive cervical lesions from all three studies could be fairly compared, detection rates for all three studies were calculated in an identical manner, using the following formula:
Detection rate for biopsy-confirmed pre-invasive cervical lesions=(# of test-positive women with biopsy-confirmed high-grade squamous intraepithelial lesions)/(# of women tested).
‡Denominator values for detection rates of biopsy-confirmed preinvasive cervical lesions in the Mumbai randomised trial were obtained from the following statement, published in 2010:2 ‘Out of 75 360 eligible women listed in the screening arm 51 145 (67.87%), 41 354 (57.84%) and 36 643 (54.26%) women participated in the first, second and third screening rounds for cervix cancer’.
§Numerator values for detection rates of biopsy-confirmed preinvasive cervical lesions in the Mumbai randomised trial were obtained from the following statement, published in 2010:2 ‘HSIL [high-grade squamous intraepithelial lesion] and LSIL [low-grade squamous intraepithelial lesion] cases were 18 and 62 in the first round, 8 and 49 in the second round, and 18 and 24 in the third round’.
¶Publications from the Mumbai randomised trial2, 3 do not report the number of women tested or the number of preinvasive cervical lesions detected during the fourth intervention round.
**Numerator and denominator values for the detection rate of biopsy-confirmed preinvasive cervical lesions for visual inspection with acetic acid in the Mumbai cross-sectional study were obtained from numbers presented in Rows 2 and 3 of the table labelled ‘Results of screening tests compared with final disease status established by the reference standard’ in a 2005 publication.15
††Numerator and denominator values for the detection rate of biopsy-confirmed pre-invasive cervical lesions for visual inspection with acetic acid in the Dindigul randomised trial were obtained from numbers presented in Row 4 of the table labelled ‘Screening findings by age in the intervention group’ in a 2007 publication.4
low detection rates for preinvasive cervical lesions reported from the Mumbai trial (table 1), as confirmed by Mumbai trial investigators in 2013.\textsuperscript{14}

From 2001 to 2003, the Bill & Melinda Gates Foundation funded a cross-sectional study of cervical screening in Mumbai.\textsuperscript{15} The Mumbai randomised controlled trial and the Mumbai cross-sectional study were performed on the same population by the same principal investigator. Detection rates for preinvasive cervical lesions using visual inspection with acetic acid, as reported from the Dindigul trial, were comparable to detection rates for preinvasive cervical lesions using visual inspection with acetic acid, as reported from the Mumbai cross-sectional study (table 1). Therefore, prevalence rates of preinvasive cervical lesions among the populations of Mumbai and Dindigul were comparable.

However, detection rates for preinvasive cervical lesions from the Mumbai trial were up to 45-fold lower than detection rates for preinvasive cervical lesions from either the Mumbai cross-sectional study or from the Dindigul trial (table 1). Since prevalence rates of preinvasive cervical lesions among the populations of Mumbai and Dindigul were comparable, the extraordinary difference in detection rates for preinvasive cervical lesions between the Mumbai trial and the Dindigul trial must be attributable to differences between the interventions actually studied during either trial.

The intervention actually studied during the Mumbai trial
As part of a journalistic investigation,\textsuperscript{16} one of the authors (REO) submitted US Freedom of Information Act requests to the US National Cancer Institute that produced 454 pages of redacted documents related to the Mumbai trial, which were posted to a Dropbox account for review by readers of this article.\textsuperscript{17} The November 1999 US National Cancer Institute grant renewal application states that, at the outset of the Mumbai trial, women in the intervention arm were to receive ‘visual inspection of the cervix’ (ref. 17, p. 43) in order to determine whether four intervention rounds of ‘visual inspection’, compared with no-screening, would be ‘effective in down-staging the disease and eventually lead to reduction in mortality’ (ref. 17, p. 5). According to the November 1999 grant renewal application, reduction in the incidence of invasive cervical cancer was not an original objective of the Mumbai trial (ref. 17, pp. 5 and 40).

Documents obtained through the US Freedom of Information Act disclose that the intervention actually studied during the Mumbai trial did not effectively detect preinvasive cervical lesions because that intervention began as a ‘visual inspection’ test, and performed as if it remained a ‘visual inspection’ test for the duration of the Mumbai trial.

During the 1980s, ‘visual inspection’ of the cervix (also referred to as ‘unaided visual inspection’) was proposed as an invasive cervical cancer control strategy for resource-limited settings, because it was thought that searching for therapeutically controllable invasive cervical cancers could be more realistic than searching for preinvasive cervical lesions.\textsuperscript{18} Visual inspection consisted of naked-eye speculum examination of the uterine cervix without prior application of either acetic acid or Lugol’s iodine. Preinvasive cervical lesions are invisible to the naked eye unless acetic acid or Lugol’s iodine is first applied to the cervix. Visual inspection therefore cannot effectively detect preinvasive cervical lesions and cannot reduce incidence rates of invasive cervical cancers. The objective of visual inspection was not to reduce incidence rates of invasive cervical cancers, but to detect invasive cervical cancers at earlier stages of disease progression and to thereby perhaps reduce mortality rates of invasive cervical cancers. For that reason, ‘visual inspection’ tests were also referred to as ‘downstaging’ tests.\textsuperscript{19}

However, by 1996, Sankaranarayanan et al had concluded “our results make it appear highly unlikely that unaided visual inspection could be a useful procedure for control of cervical cancer,” because of extraordinarily low detection rates for preinvasive cervical lesions and invasive cervical cancers.\textsuperscript{20} By 1997, Sankaranarayanan had concluded “in summary, the performance of unaided visual inspection is not satisfactory to consider this as an approach for cervical cancer control in developing countries.”\textsuperscript{19}

Nevertheless, documents obtained through the US Freedom of Information Act fail to explain why the US National Cancer Institute funded an 18-year trial to study an intervention judged to be unsatisfactory, before the trial began, by the Chair of the trial’s Data Safety and Monitoring Committee. Extraordinarily low detection rates for preinvasive cervical lesions reported from the Mumbai trial are more consistent with the use of visual inspection/downstaging, and less consistent with the use of visual inspection with acetic acid, as the intervention actually studied during the Mumbai trial. The Mumbai trial scheduled four intervention rounds, rather than one intervention round, plausibly because visual inspection/downstaging had been judged ‘quite unlikely to achieve a stage shift as soon as it is introduced.’\textsuperscript{19}

The November 1999 US National Cancer Institute grant renewal application states “The visual examination of the cervix has now been modified...and the cervix is painted with 2% acetic acid before examination so as to identify more reliably acetowhite patches as suspicious. However, the modification was implemented a few months after the study was started. So that out of 21,542 women in the intervention arm who were given an examination, only 15,755 were screened by VIA [visual comparison of acetic acid staining and iodine staining].
inspection with] (2% acetic acid)” (ref. 17, p. 43). Publications from the Mumbai trial do not acknowledge the initial use of visual inspection/downstaging, or the change in study intervention from visual inspection/downstaging to visual inspection with 2% acetic acid.

However, detection rates for preinvasive cervical lesions went down, rather than up, after visual inspection with 2% acetic acid reportedly replaced visual inspection/downstaging as the intervention studied during the Mumbai trial (table 1). That finding is also more consistent with the use of visual inspection/downstaging, and less consistent with the use of visual inspection with acetic acid, as the intervention actually studied during the first three rounds of the Mumbai trial. Since publications from the Mumbai trial do not report the number of women tested or the number of preinvasive cervical lesions detected during the fourth intervention round, it is uncertain whether the fourth intervention round was actually performed.

Concerns had been raised, but not addressed, why the Dindigul trial was initiated after the Mumbai trial was already in progress, and why the Mumbai trial continued for 7 years after the Dindigul trial was halted. Documents obtained through the US Freedom of Information Act disclose that the objective of the Mumbai trial, at least initially and more likely for its entire duration, was to study the effect of visual inspection/downstaging on mortality rates of invasive cervical cancers. In contrast, the objective of the Dindigul trial was to study the effect of visual inspection with acetic acid on incidence and mortality rates of invasive cervical cancers. Differences between the objective of the Mumbai trial and the objective of the Dindigul trial explain why the Dindigul trial was initiated after the Mumbai trial was already in progress. Differences between the objective of the Mumbai trial and the objective of the Dindigul trial explain why the Dindigul trial was initiated after the Mumbai trial was already in progress. Differences between the objective of the Mumbai trial and the objective of the Dindigul trial explain why the Dindigul trial was initiated after the Mumbai trial was already in progress.

The effect of visual inspection/downstaging on mortality rates

An important unresolved concern regarding the Mumbai trial is how cervical screening apparently reduced mortality rates of invasive cervical cancers without reducing incidence rates of invasive cervical cancers.5-7 Mumbai trial investigators stated “we had observed statistically significant downstaging after three screening rounds,” which presumably caused the reduction in mortality rates of invasive cervical cancers reported by the Mumbai trial. However, Mumbai trial investigators acknowledged “an important limitation of the study is that accurate staging information was not available for 23 case patients from the screening group and 36 case patients from the control group.”9 Had it been available, accurate staging information from those 59 patients may have indicated that significant downstaging did not actually occur during the Mumbai trial. In that case, the interventions provided could not have caused reported reductions in mortality rates of invasive cervical cancers, because, in that case, the interventions provided, which did not reduce incidence rates of invasive cervical cancers, would also not have caused significant downstaging.

Moreover, documents obtained through the US Freedom of Information Act disclose major discrepancies between clinical staging data reported to the US National Cancer Institute in 2004 and clinical staging data published in 2010. The October 2004 US National Cancer Institute grant renewal application includes data tables showing the clinical stages at which invasive cervical cancers were diagnosed, in the intervention arm (ref. 17, p. 255) and in the control arm (ref. 17, p. 256). Clinical staging data from the intervention arm reported to the US National Cancer Institute in 2004, compared with the same data published in 2010, are presented in figure 1. Clinical staging data from the control arm reported to the US National Cancer Institute in 2004, compared with the same data published in 2010, are presented in figure 2.

All discrepancies documented in figures 1 and 2 support the hypothesis that the intervention provided during the Mumbai trial caused significant downstaging. No discrepancies contradict that hypothesis. For example, for the third intervention round, investigators reported to the US National Cancer Institute in 2004 that 60% of invasive cervical cancers were diagnosed in early stages, and 40% were diagnosed in late stages (figure 1). For the same intervention round, investigators published in 2010 that 100% of invasive cervical cancers were diagnosed in early stages, and 0% were diagnosed in late stages (figure 1). None of these discrepancies were acknowledged or explained in publications from the Mumbai trial.

In 2015, one of the authors (EJS) communicated allegations of data falsification to the US Office of Research Integrity, which initiated an investigation into the Mumbai trial. When the US Office of Research Integrity determines that research misconduct has occurred, it publishes its determinations in the US Federal Register. When there is no finding of research misconduct, there is no public notice and US Office of Research Integrity records remain confidential. One year after the US Office of Research Integrity initiated its investigation, no determinations regarding the Mumbai trial had been published in the US Federal Register. Subsequently, one of
the authors (EJS) submitted a US Freedom of Information Act request to the US Department of Health and Human Services that produced six pages of redacted documents pertaining to the US Office of Research Integrity investigation, which were posted to a Dropbox account for review by readers of this article.22 Those documents show that the US Office of Research Integrity determined data falsification had not occurred because ‘many factors were responsible’ for the observed discrepancies (ref. 22, p. 5). However, because redacted documents obtained through the US Freedom of Information Act do not specify any of the ‘many factors’ responsible for observed discrepancies, and because clinical staging information was not available from 59 patients with invasive cervical cancer in the Mumbai trial. No discrepancies contradict that hypothesis. Reasons for discrepancies in total numbers of cases during each screening round are unknown. None of these discrepancies were acknowledged in publications from the Mumbai trial. 2 3 The findings of our study support the validity of the 2012 determinations by the US Office for Human Research Protections. It is implausible that the 75 360 trial was funded by the Bill & Melinda Gates Foundation, rather than by the US government, the Osmanabad trial is not subject to oversight by the US Office of Research Integrity.

Congressional oversight of the Mumbai trial
In 2011, one of the authors (EJS) submitted concerns regarding the Mumbai trial to the US Presidential Commission for the Study of Bioethical Issues and to the US Office for Human Research Protections. The US Presidential Commission did not address these concerns. The US Office for Human Research Protections conducted an investigation and determined in 2012 that consent had been improperly obtained from Mumbai trial participants because those women had not been provided with adequate information to understand differences between research procedures and Pap smears.26 The findings of our study support the validity of the 2012 determinations by the US Office for Human Research Protections. It is implausible that the 75 360

Table – 5: Staging of Cervix cancer cases at diagnosis (Intervention Arm)

| Screening Round | Stage (CIS + I + II) | Stage (III + IV) | Total |
|-----------------|----------------------|------------------|-------|
| 1st Screening (I C 1 – 10) | 07 (35%) | 13 (65%) | 20 |
| 2nd Screening (I C 1 – 10) | 14 (50%) | 14 (50%) | 28 |
| 3rd Screening (I C 1 – 6) | 09 (50%) | 06 (40%) | 15 |
| 4th Screening (I C 1 – 5) | 02 (100%) | -- | 02 |

Table – 6: Staging of Symptomatic referrals at diagnosis (cervix-control arm)

| HE/monitoring rounds | Early stage (0 + I + II) | Late stage (III + IV) | Staging not available | Total |
|----------------------|--------------------------|-----------------------|-----------------------|-------|
| One                  | 16 (80.00%)              | 4 (20.00%)            | 0                     | 20 |
| Interval cancers     | 7 (58.33%)               | 5 (41.67%)            | 2                     | 14 |
| Two                  | 10 (88.33%)              | 2 (16.67%)            | 0                     | 12 |
| Interval cancers     | 12 (60.00%)              | 8 (40.00%)            | 2                     | 22 |
| Three                | 17 (100.00%)             | 0                     | 0                     | 17 |

Table – 7: Staging of Cervix cancer cases at diagnosis (Control Arm)

| Health education / Surveillance Rounds | Stage (CIS + I + II) | Stage (III + IV) | Total |
|---------------------------------------|----------------------|------------------|-------|
| Round 1 (IC 1 – 10)                   | 03 (37.5%)           | 08 (62.5%)       | 08    |
| Round 2 (IC 1 – 10)                   | 06 (42.9%)           | 08 (57.1%)       | 14    |
| Round 3 (IC 1 – 6)                    | 06 (50%)             | 06 (50%)         | 12    |
| Round 4 (IC 1 – 5) Ongoing            | 02 (60%)             | 02 (50%)         | 04    |

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women recruited into the intervention arm of the Mumbai trial would have agreed to four rounds of visual inspection/downstaging if they had been informed about differences between visual inspection/downstaging and Pap smears, and if they had been informed that visual inspection/downstaging was an unsatisfactory intervention for cancer control. It is implausible that the 76,178 women recruited into the no-screening arm of the Mumbai trial would have agreed to receive no-screening from 1997 to 2015 if they had been informed about differences between no-screening and Pap smears. It is also implausible that women recruited into the no-screening arms of the Dindigul and Osmanabad trials would have agreed to receive no-screening if they had been informed about differences between no-screening and Pap smears. However, because the Dindigul and Osmanabad trials were funded by the Bill & Melinda Gates Foundation, rather than by the US government, those trials are not subject to oversight by the US Office for Human Research Protections, the US Office of Research Integrity, the US Presidential Commission for the Study of Bioethical Issues or the US Freedom of Information Act.

Data summarised in Table 1 establish that none of the 75,360 women in the intervention group of the Mumbai trial received cervical screening tests that effectively detected preinvasive cervical lesions. It is unlikely that those women will be offered additional screening tests after the close of the Mumbai trial. After the close of the Mumbai trial, it is uncertain whether the 76,178 women in the control group will be offered cervical screening tests that effectively detect preinvasive cervical lesions, such as those studied during the Mumbai cross-sectional study, or cervical screening tests that do not effectively detect preinvasive cervical lesions, such as those studied in the intervention group of the Mumbai trial.

In 2012, one of the authors (EJS) shared US Office of Human Research Protection determinations regarding the Mumbai trial with the office of US House Democratic Leader Nancy Pelosi, whose Senior Health Policy Advisor, Wendell Primus, arranged a conference call in 2013 among leaders at the US National Cancer Institute and staff of the US House Energy and Commerce Committee, which oversees the budget of the US National Cancer Institute. Subsequently, one of the authors (EJS) submitted a US Freedom of Information Act request to the US National Institutes of Health that produced 221 pages of redacted documents pertaining to the 2013 conference call, which were posted to a Dropbox account for review by readers of this article.

Those documents disclose that US National Cancer Institute leaders avoided accountability for the Mumbai trial by making false and misleading statements to Congressional oversight staff. For example, US National Cancer Institute leaders stated “there were no issues with the science” of the Mumbai trial (ref. 29, p. 10). US National Cancer Institute leaders did not inform Congressional oversight staff that science had established the superiority of cervical screening, compared with no-screening, long before the Mumbai trial began. US National Cancer Institute leaders did not inform Congressional oversight staff that the Mumbai trial studied an intervention that Sankaranarayanan had proven unsatisfactory for cancer control before the Mumbai trial began; that, by design, the unsatisfactory intervention studied had failed to prevent invasive cervical cancers; or that the unsatisfactory intervention studied may not actually have reduced mortality rates of invasive cervical cancers.

US National Cancer Institute leaders stated “We have reviewed the translated version of the 14-page consent form and are confident that the women were informed to the extent possible. Most of the women were illiterate” (ref. 29, p. 9). It is implausible that a 14-page written consent form can adequately inform illiterate women. Moreover, US National Cancer Institute leaders did not inform Congressional oversight staff that the US Office for Human Research Protections had discovered major discrepancies between the informed consent form submitted with US National Cancer Institute grant applications and the informed consent form actually used during the Mumbai trial. For example, the informed consent form submitted with US National Cancer Institute grant applications included information that Pap smears are standard cervical screening procedures in ‘developed countries’; that Pap smears are available in India and that women could obtain Pap smears on their own if they did not wish to participate in the Mumbai trial. However, such critical information was not present in the informed consent form actually used in the Mumbai trial.

Nevertheless, US National Cancer Institute leaders left Congressional oversight staff ‘glad to be fully informed, and gratified to learn that the study has had such positive impacts’ (ref. 29, p. 10) Subsequently, despite determinations by the US Office for Human Research Protections, US National Cancer Institute leaders declared to the global public, through the Associated Press, “We looked at the ethics [of the Mumbai trial] very carefully and felt them to be sound.” Despite determinations by the US Office for Human Research Protections, the principal investigator of the Mumbai trial received the 2014 Humanitarian Award from the American Society of Clinical Oncology. In 2017, the Supreme Court of India declared that women had given their voluntary informed consent to participate in the Mumbai, Dindigul and Osmanabad trials, and dismissed public interest litigation filed on behalf of these vulnerable study participants.

**CONCLUSION**

In conjunction with determinations by the US Office for Human Research Protections, the findings of our study contradict assurances provided by the US Presidential Commission for the Study of Bioethical Issues to President Barack Obama that regulations pertaining to
global health research supported by the US government ‘protect people from avoidable harm or unethical treatment’. Research supported by the Bill & Melinda Gates Foundation should be subject to the same level of transparency as research supported by the US government. The US National Cancer Institute, in conjunction with other global health organisations, should develop policies to compensate victims of unethical global health research. As a first step, all surviving participants of the Mumbai trial, from the intervention and control arms, should finally receive cervical screening tests that effectively detect preinvasive cervical lesions, as documented by detection rates for biopsy-confirmed preinvasive cervical lesions.

Proponents of visual screening tests emphasise that close monitoring of detection rates for biopsy-confirmed preinvasive cervical lesions is essential to maintain adequate quality control of visual screening methods. The findings of our study reinforce the critical necessity of carefully monitoring detection rates for biopsy-confirmed preinvasive cervical lesions to prevent the failure of cervical screening efforts in low-income and middle-income countries, irrespective of the screening technologies used.

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