Research Project: Early Detection of Common Cancers in Women in India  
Principal Investigator: Dr. Surendra Srinivas Shastri  
HHS Protocol Number: 5R01CA074801

Dear Dr. Suba:

The Office for Human Research Protections (OHRP) has completed our evaluation of human subject protections in the research referenced above.

Based upon our evaluation, we made the following determinations relative to protections for human subjects in this research at Tata Memorial Hospital (TMH).

Determinations regarding the above-referenced research

1. You alleged and we determined that subjects were not adequately informed of the alternative procedures or courses of treatment regarding screening for breast cancer or cervical cancer, namely, mammography and Pap testing. This was in violation of Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(4) which require the disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, as part of informed consent.

2. We determined that the subjects were not provided, in writing, with information about the possible alternative of seeking breast or cervical cancer screening outside of the research, as required by HHS regulations at 45 CFR 46.116(a)(4), 46.117(b)(1).

Corrective Action: We acknowledge that the TMH IRB modified their standard operating procedures (SOPs) to refer to relevant HHS regulations at 45 CFR 46.116. We also acknowledge that the TMH IRB unanimously decided that the study subjects should be informed about modalities like mammography and Pap smear, and the differences from the study related procedures. The IRB unanimously agreed that this information could be provided verbally, and waived the requirement for written informed consent in this regard. We also acknowledge that the IRB unanimously decided that the PI should offer screening for cervical cancer by Visual Inspection with Acetic Acid (VIA) to subjects in the control group.

3. We also made determinations related to IRB failure to conduct continuing review of research at least once per year, failure of the IRB to meet the quorum requirement for one IRB meeting, and failure to maintain minutes of IRB meetings.
Corrective Action: We acknowledge that the TMH written IRB SOPs have been revised to address these issues.

Regarding your allegations that ongoing measurements of cervical cancer death rates appear to be scientifically gratuitous and appear to fail to satisfy additional ethical requirements of equipoise and that unscreened control groups of women are not ethically justified, we did not present these allegations to the institution because there did not appear to be violation of the HHS human subject protections regulations. In that regard, we also note that the study was a test of the entire human services program related to these screenings and it was not known beforehand whether or not these practices could be implemented effectively in this low-resource setting.

We also did not evaluate your allegations regarding Hybrid Capture 2® studies, as the studies were not funded by HHS, but we forwarded your allegations to the Food and Drug Administration.

We have determined that these corrective actions are appropriate under the institution's Assurance and anticipate no further involvement in this matter.

We appreciate your concern about the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,
Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

Eric:
We have issued determinations in this evaluation; the letters can be found on our website at:
http://www.hhs.gov/ohrp/detrn_letrs/YR12/jul12d.pdf

You should contact the FDA regarding the status of their evaluation.

Sincerely,
Kristina
Kristina C. Borror, Ph.D.
Director
Kristina, do you have an idea of how much more time your review and the FDA review will require?  Thanks again.

Eric Suba

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Dear Dr. Suba:

The Office for Human Research Protections (OHRP) has received additional information regarding the research involving cancer screening in India conducted by Tata Memorial Hospital that you inquired about and are focusing our investigation on your allegations related to informed consent issues. We will investigate any other appropriate issues that come up during our investigation.

You also expressed concerns about another study, funded by the Bill & Melinda Gates Foundation. OHRP does not have authority over that study since it did not involve any HHS support. As I noted previously, OHRP has referred these allegations to the Food and Drug Administration for review.

OHRP appreciates your concern about the protection of human research subjects. Please do not hesitate to contact me at any time should you have any questions or wish to provide additional information.
Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
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Fax: (240) 453-6909

From: Eric.Suba@kp.org [mailto:Eric.Suba@kp.org]
Sent: Tuesday, April 17, 2012 7:25 PM
To: Borror, Kristina C (HHS/OASH)
Subject: RE: May 18th Presidential Commission Meeting in NYC

Do you have an idea of how much more time your review will require?

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We are still looking into it.

From: Eric.Suba@kp.org [mailto:Eric.Suba@kp.org]
Sent: Friday, April 06, 2012 4:54 PM
To: Borror, Kristina C (HHS/OASH)
Subject: RE: May 18th Presidential Commission Meeting in NYC

Kristina, is there any additional information available yet concerning your review of these studies? Thanks again.
Eric Suba

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"Borror, Kristina C (HHS/OASH)" <Kristina.Borror@hhs.gov>

01/26/2012 06:45 AM

Thank you for the information.

Kristina

From: Eric.Suba@kp.org [mailto:Eric.Suba@kp.org]
Sent: Tuesday, January 17, 2012 5:16 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Bonham, Valerie (HHS/PCSBI); Menikoff, Jerry (HHS/OASH); adampm@upenn.edu; Yoo, Esther (HHS/PCSBI); Viers, Hillary (HHS/PCSBI)
As noted below, additional federal funding for the controversial India cervical screening studies was awarded on August 23, 2011. The current study description notes that:

"Significant downstaging of cervical cancer by VIA is already evident. The trial data safety and monitoring board (DSMB) has considered this, but decided that we should continue with the follow-up as planned, till we reach the required decision point."

In other words, it appears that the India investigators asked the DSMB whether continuation of the controversial no-screening arm was still required in the face of the investigators' own finding of clear-cut health benefits from screening. Apparently, the DSMB responded by instructing the India investigators to continue to measure cervical cancer death rates among unscreened Indian women of lowest socioeconomic status.

I trust that you are aware of this significant observation.

Eric J. Suba, M.D.
President and Executive Director
The Viet/American Cervical Cancer Prevention Project
http://www.vietnamcervicalcancer.org/index.php
Abstract Text:

DESCRIPTION: By 2020, an estimated 128,538 new cases of breast cancer and 7,023 deaths due to it, and an estimated 20,549 deaths from cervical cancer would occur in India, contributing to 20% and 30% of the global burden of cervical cancer and mortality. Currently, there is no national breast and cervical cancer screening program in India. Primary care facilities are largely non-existent and the medical care is sub-optimal. The primary aim of this ongoing cluster randomized controlled trial, conducted in urban slum women aged 35-64 years, in Mumbai, India, is to test the hypothesis that using affordable, sustainable, and culturally acceptable techniques, i.e., Clinical Breast Examination (CBE) and Visual Inspection with Acetic Acid (VIA) for primary case finding, followed by screening with mammography and cervical cytology, can reduce breast and cervical cancer incidence. The secondary aims of the trial are to: a) Estimate the cost and resource needs for conducting community-based cancer screening by CBE and VIA, and b) To study the behavioral, cultural, and psychological factors affecting participation of women in such programs. The findings are planned: a) planned analysis of process measures supports clearly the feasibility and acceptability, with excellent screening participation, and b) we have an excellent mechanism for capturing the events in the screening and control groups, and c) Significant evidence. The trial data safety and monitoring board (DSMB) has considered this, but decided that we should continue with the follow-up as planned, till the data analysis is completed. The progress of this trial to date clearly demonstrates the potential of cervical cancer control policies not only in India but also worldwide. We anticipate that continued follow-up will result in the required number of endpoints.

Public Health Relevance Statement:

This cluster randomized controlled trial, involving 15,1538 socially disadvantaged women (slum dwellers) aged 35-64 years, studies the efficacy of screening for breast and cervical cancer performed by female primary health workers (FPHWs). The progress of this trial to date clearly demonstrates the great potential of its results to guide breast and cervical cancer control policies not only in India but also worldwide.

Project Terms:

Acetic Acid; Affect; aged; base; Behavioral; Breast; Breast cancer; Breast Cancer Detection; Breast cancer Early Detection; cancer Control; cancer education; cervical; Clinical; clinical efficacy; Clinical Trials Data Monitoring Committees; Communities; Compliance behavior; Control Groups; cost; Data; Data Analyses; Diagnosis; Female; follow-up; Health; Incidence; India; malignant breast neoplasms; Malignant neoplasms of cervix uteri; Malignant Neoplasms; Mortality Vital Statistics; Psychological Factors; public health relevance; Publishing; Randomized Controlled Trials; Resources; Screening procedure; Slum; Techniques; Training;
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----- Forwarded by Eric Suba/CA/KAIPERM on 01/17/2012 01:52 PM -----

Eric Suba/CA/KAIPERM

To
Dear Dr. Borror,

Thank you for the follow up information. I am grateful for your efforts. Please keep me posted.

Eric Suba

We have also forwarded your allegations to the US Food and Drug Administration (FDA).

From: Borror, Kristina C (HHS/OASH)
Sent: Monday, December 12, 2011 4:55 PM
To: 'Eric.Suba@kp.org'
Subject: RE: May 18th Presidential Commission Meeting in NYC

Dear Dr. Suba:

The Office for Human Research Protections (OHRP) has received your May 31, 2011 email concerning research involving cervical cancer prevention being conducted in India. I sincerely apologize for the delay in responding to you.

OHRP has responsibility for oversight of compliance with the U.S. Department of Health and Human Services (HHS) regulations for the protection of human research subjects (see 45 CFR Part 46 at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html). In carrying out this responsibility, OHRP evaluates, at OHRP’s discretion, substantive allegations of noncompliance involving human subject research projects conducted or supported by HHS or that are otherwise subject to the regulations (see OHRP memorandum dated October 14, 2009 at

We are reviewing information we have received from the funding agency and we have requested additional information.

OHRP appreciates your concern about the protection of human research subjects. Please do not hesitate to contact me at any time should you have any questions or wish to provide additional information.

Sincerely,

Kristina C. Borror, Ph.D.
 Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

From: Eric.Suba@kp.org [mailto:Eric.Suba@kp.org]
Sent: Tuesday, May 31, 2011 2:18 PM
To: Menikoff, Jerry (HHS/OASH)
Cc: Borror, Kristina C (HHS/OASH); Bonham, Valerie (HHS/PCSBI); adampm@upenn.edu; m.zecevic@lancet.com
Subject: May 18th Presidential Commission Meeting in NYC

Dear Dr. Menikoff:

I attended your excellent and informative presentation at the May 18th meeting of the Presidential Commission for the Study of Bioethical Issues in New York City. Valerie Bonham, Adam Nelson, and Maja Zecevic, who also attended the May 18th meeting, are cc’d on this message.

My CV is attached. I am a 1980 graduate of Princeton University and a 1984 graduate of Washington University Medical School in Saint Louis. Cervical cancer prevention in developing countries is my special career interest. I provided comment at the May 18th meeting regarding controversial studies of cervical cancer prevention being conducted in India among women of lowest socioeconomic status with support from the U.S. National Cancer Institute(1) and the Bill & Melinda Gates Foundation.(2) These studies include measurements of cervical cancer death rates among large numbers of unscreened women. Concerns about these death-rate measurements have previously been published in various peer-reviewed journals and are outlined in the attached pdf file. Please consider that:

1. These death-rate measurements appear to be scientifically gratuitous and, in addition, do not appear to satisfy ethical requirements of equipoise and informed consent.
2. Methodological bias has provided a false appearance of scientific meaning to these death-rate measurements.
3. A false appearance of scientific meaning from these death-rate measurements has been used to publicize misleading claims about a proprietary cervical screening test that is unaffordable to the Indian population among whom it was studied.
4. Potential financial conflicts of interest exist between study sponsors and the manufacturer of the
proprietary cervical screening test about which misleading claims have been publicized.

I would be grateful if your Office would review these concerns, which have also been shared with the Presidential Commission. I will include the responses from your Office and from the Presidential Commission in a future peer-reviewed publication, the goal of which will be to provide some closure to the longstanding, unresolved debate regarding these controversial studies.

Thank you for your consideration of this request.

Eric J. Suba M.D.
President and Executive Director
The Viet/American Cervical Cancer Prevention Project
eric.suba@kp.org
415.922.2364

References:


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