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July 5, 2012

Dr. Anil K. D'cruz, M.S.  
Director  
Tata Memorial Hospital  
Dr. E. Borges Road  
Parel  
Mumbai, Maharashtra  
INDIA

**RE: Human Research Protections Under Federalwide Assurance FWA-6143**

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

Dear Dr. D'cruz:

Thank you for your June 4, 2012 report in response to our May 7, 2012 request that Tata Memorial Hospital (TMH) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on review of your response, we make the following determinations:

A. Determinations regarding the above-referenced research

- (1) We have 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. HHS regulations at 45 CFR 46.116(a)(4) 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. The research study involved offering the subjects a form of screening for breast and cervical cancer that is different from mammography and Pap testing which are considered the "gold standard" for such screening. It has been reported that the medical social worker responsible for obtaining the consent from subjects

gave an unbiased verbal listing of nearby screening facilities providing Pap smears and mammography, which may be free or may require payment.

However, based on our review of the materials used to brief the prospective subjects about the research study, we believe that subjects were not provided with adequate information to understand the differences between the research procedures and mammography and Pap smears. Understanding what their alternatives are is key to the subjects' ability to make an informed decision about whether or not to participate in a research study. While an institutional review board (IRB) reviewing this study would have the authority, under appropriate circumstances, to have modified or waived this regulatory requirement, we do not find any evidence that the IRB modified or waived this requirement for the above-referenced research.

- (2) We have 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. Obtaining informed consent is required by the HHS regulations at 45 CFR 46.111(a)(4). Disclosing appropriate alternative procedures or courses of treatment as part of informed consent is required by the HHS regulations at 45 CFR 46.116(a)(4). Using a written consent document that embodies the elements of informed consent identified in 45 CFR 46.116 is required by HHS regulations at 45 CFR 46.117(b)(1). We note that the HHS regulations at 45 CFR 46.116 allow the IRB to approve a waiver or alteration of informed consent under certain conditions, and that the regulations at 45 CFR 46.117 allow the IRB to approve the use of a short form or a waiver of documentation of informed consent (e.g., to allow the information to be provided to subjects verbally, but not in written form, and as noted above, there is a claim that the subjects were indeed given this information verbally), but there is no evidence that the IRB chose to utilize these options.

We note that the 2010 grant application indicates that subjects were "made aware of the availability of breast and cervical cancer screening methods like mammography and Pap smear" and the model informed consent document from the 2005 grant application stated "The standard screening procedures for cervix and breast cancers are Pap smear and Mammography, in developed countries. Such facilities are also available in some centres in India and you may choose to undergo these tests on your own, if you do not wish to participate in this study." However, a translated copy of the informed consent document actually used in the study that we were provided did not include this language. When such information is only provided verbally, subjects may not recall the information later, or may not fully understand what is told to them orally. Therefore the default is that such information must be provided in writing, unless the IRB finds legitimate reasons to waive the regulatory

requirement that informed consent be documented in order to allow the information to be provided verbally.

- (3) We have determined that the IRB failed to conduct continuing review of research at least once per year. The HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. We note that the study received HHS support from 1997-2003 and 2005 to the present; however continuing review did not occur during the following years: 2000, 2003, 2006, and 2008. Continuing review by the IRB is important, in part, to determine whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, and that the safeguards in place at the time of original approval are, in fact, adequate to ensure the safety of subjects.
- (4) We have determined that minutes of IRB meetings do not exist (or were not provided to our office upon request) for the following meetings: September 25, 1998; June 22, 1999; November 17, 1999; August 17, 2001; June 17, 2002; February 24, 2004; and that minutes of IRB meetings that were provided to us are not in sufficient detail to show the vote on actions taken by the IRB including the number of members voting for, against, and abstaining. The HHS regulations at 45 CFR 46.115(a)(2) require that meeting minutes including this information be written and maintained. It is important to maintain documentation of IRB actions and discussions so that the institution has a record of what transpired at the meetings, what decisions were made and actions taken. This is also important for future decision-making about a particular project.
- (5) We have determined that the IRB failed to meet the quorum requirement for the IRB meeting of April 11, 2007. The HHS regulations at 45 CFR 46.108(b) require that research be reviewed at convened meetings at which a majority of the members of the IRB are present, except when an expedited review procedure is used. We note that our records indicate that the IRB had 16 members during this time, but only 3 members were present at this meeting.

**Required Action:**

Please provide us with responses to the above determinations by August 10, 2012, including a corrective action plan for each of our determinations. Feel free to contact me if you would like guidance in developing a corrective action plan.

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Dr. Anil K. D'cruz, M.S.-- Tata Memorial Hospital

July 5, 2012

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

Sincerely,

Kristina C. Borrer, Ph.D.

Director, Division of Compliance Oversight

cc:

Dr. Rajendra A. Badwe, Director, Tata Memorial Centre

Dr. Madhuri Gore, Chairperson, Human Ethics Committee-I, Tata Memorial Hospital

Dr. Urmila Thatte, Chairperson, Human Ethics Committee-II, Tata Memorial Hospital

Dr. Surendra Srinivas Shastri, Tata Memorial Hospital

Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)

Dr. Joanne Less, FDA

Dr. Sherry Mills, National Institutes of Health (NIH)

Mr. Joseph Ellis, NIH

Dr. Harold Varmus, Director, National Cancer Institute, NIH