An open letter to the Presidential Commission for the Study of Bioethical Issues.

Concerning the Presidential Commission's Review of the Ethics of Human Medical Experiments, and Repetition of Tuskegee & Guatemala and Ongoing Unethical Practices

Amy Guttmann, PhD, Chair, and Commission Members
Presidential Commission for the Study of Bioethical Issues
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Dear Dr. Guttmann and Commission Members:

President Obama's charge to the Commission is to 1) review the clinical research conducted by the Tuskegee and Guatemala studies and to 2) determine whether ethical violations currently or potentially exist in the conduct of clinical research sponsored by the U.S. government in resource-poor countries. If unbiased determinations are to be made, the reviewers and invited presenters of the commission must be free of potential conflicts of interest. Our review of certain NIH-sponsored research studies, and our review of the brief, publically-available biographies of commission members and reviewers, raise questions as to whether some individuals may have potential conflicts of interest in reaching unbiased conclusions. http://www.whitehouse.gov/the-press-office/2010/11/24/presidential-memorandum-review-human-subjects-protection

We urge you in your capacity as Chair of the President's Commission to consider the issue of conflicts of interest and to take whatever appropriate remedial action is required to eliminate any such conflicts before the Commission proceeds further in its investigation, and secondly, to take heed of current NIH-funded research projects which may have committed or are currently committing ethical violations that are uncomfortably reminiscent of the Tuskegee and Guatemala projects.

Issues of concern directed to the Commission members.

Conflict of Interest Concerns and Representation Issues

Conflicts of interest may arise when the institutions represented by Commission members or members themselves receive direct or indirect benefit from clinical research studies. It is our understanding that the U.S. Government requires individuals participating in U.S. Government committees to reveal actual or potential conflicts of interest, whether individuals come from academic or industry backgrounds. Universities, clinical research groups, individual investigators and others who participate in clinical research, whether in the U.S. or in resource-poor countries, often receive significant income from government agencies such as NIH as well as from pharmaceutical organizations. The financial and career benefits in conducting international research creates a potential, if not actual, conflict of interest for some Commission members charged with investigating current ethical practices.

As pointed out by several of the commission members, there is a definite shift of clinical research to the more easily accessible and greater numbers of research subjects in resource-poor countries, both by industry and importantly also by academic clinical researchers. A commission member pointed out that this creates a situation of potential conflict of interest and the necessity of achieving a balanced and independent review of the ethical standards for the conduct of clinical research. The mere size of these studies, involving thousands of research subjects and millions of dollars, naturally make it difficult for invested researchers to make objective and unbiased decisions as to whether studies conform to all international ethical standards, as well a whether a study should be stopped because it has become unethical to continue.

Given the clear potential for conflict of interest, each Commission member should make available for the public record a complete CV and a potential conflict or non conflict of interest declaration, as well as a list of potentially conflicting activities. These disclosures should include financial disclosures. The declaration should also state whether the Commission member has him/herself ever been subject to ethical review for studies performed. (One committee member has participated in a vaccine trial that was later questioned by HIV advocates as to scientific and ethical integrity. Another committee member is also a member of the Institute of Medicine, which recused itself from review of the Guatemala study.)

The current composition of the Committee is dominated by U.S. academically-based members. We believe that it is important that the interests of vulnerable populations be represented as well. In order to do so, it would be best if there were Commission members with direct on-the-ground research experience in resource-poor countries. Since it may not be possible to add new Commission members at this time, we urge you to invite testimony from experts with in-depth clinical research experience in resource-poor countries who can adequately represent the interests of the subjects and communities at risk.

We make the above requests because we strongly believe, and we are confident that you will agree, that the integrity of the Commission's findings, conclusions and recommendations must not be tainted by any actual or apparent conflicts of interest of any of its members or institutions and further, that the Commission's conclusions represent a thorough vetting of ethical issues of concern by advocates and experts having in-depth experience with vulnerable populations in resource-poor countries.

Tuskegee, Guatemala, HPTN 046 AND 052: NIH Unethical Practices from 1932 to the Present and Ongoing.

Exploitation of vulnerable subjects, fraud and deception, denial of treatment, sub-standard of care treatment and intentional infection causing harm to research subjects are all common themes of Tuskegee, Guatemala and more recently, the NIH-funded HPTN 046 and HPTN 052 research experiments.

Tuskegee
http://www.brown.edu/Courses/Bio_160/Projects2000/Ethics/TUSKEGEESYPHILISSTUDY.html

- Deception: Tuskegee study subjects suffering from syphilis were often deceived, lead to believe they were receiving medication when in fact they were given nothing more than aspirin. Spinal taps were represented to be injections.
- Failure to obtain informed consent
- Vulnerable Subjects: The majority of the subjects were vulnerable, illiterate and impoverished Blacks of Macon County, Georgia.
- Withholding of Treatment: Some subjects received treatment, but most received no treatment in order to allow the physicians to observe how untreated syphilis affected the infected subjects. Treatment was withheld, notwithstanding knowledge that untreated syphilis could lead to the tertiary stage with the infection spreading to the brain, nervous system, heart, skin and bones, and could ultimately lead to death.
- Intentionally allowing disease to progress. Although subjects were not intentionally infected, to withhold treatment and allow the disease to progress unimpeded posed ethical issues not unlike those posed by the intentional infection practices in Guatemala.
- Failure to notify sexual contacts. Sexual contacts were not notified of their risk of infection, tested for infection or offered treatment if infected.

Guatemala
http://www.wellesley.edu/WomenSt/Synopsis%20Reverby%20%27Normal%20Exposure%27.pdf

- Intentional infection of vulnerable subjects (prisoners) and inoculation of mental patients with syphilis. The USPHS paid infected prostitutes to have sex with prisoners in order to infect them and to study penicillin's efficacy as a

prophylaxis and its impact upon disease after infection. To gain cooperation of the asylum officials, supplies were offered, such as Dilantin, a refrigerator for biological materials storage, a motion picture projector, dining room supplies, etc.

- Deception: Asylum officials initially believed that the inoculation they were given to administer was simply another type of drug. Neither the prisoners nor the mental patients were informed that they were being infected with a potentially lethal disease.
- Vulnerable Subjects: Clearly, prisoners and mental asylum patients are among the most vulnerable subjects that can be exploited.
- Selection of a country where inferior treatment and care were acceptable. Guatemala was selected as the study site because the study could not be performed in the U.S. and the Health Ministry gave no objections to performing a study that placed the Guatemalan research subjects at risk.
- Failure to notify sexual contacts. Non-study sexual partners were not notified of their risk of infection, were not tested for infection or offered treatment if infected.

HPTN 046 AND HPTN 052

The National Institutes of Health has sponsored studies performed on poor and vulnerable populations in developing countries on 1) the prevention of HIV transmission between discordant couples (HPTN 052) and 2) Prevention of Mother to Child Transmission of HIV (PMTCT) (HPTN 046). Such studies could not have been ethically performed in the U.S. and so were outsourced to countries with lower standards of care.

HPTN 052: http://www.hptn.org/research_studies/hptn052.asp

- Deliberate withholding of treatment allowing HIV disease to progress for research purposes: The study involved evaluating individuals who were HIV infected and their sexual partners who were HIV uninfected (i.e., a discordant couple). The study design divided HIV-infected participants into immediate treatment and delayed treatment, in spite of the fact that clinical studies showed that delay in treatment resulted in disease progression, increased complications and increased mortality. The stated purpose of this study was to determine whether initiation of immediate treatment of an HIV-infected individual was associated with a reduction of HIV transmission to the uninfected partner compared to delayed treatment of an HIV-infected individual and transmission of HIV to their uninfected sexual partner. One study group was denied treatment until the CD4 count declined to 200-250 or the patient became symptomatic

with AIDS; the other study group commenced treatment at a CD4 count of 350. During the conduct of the study, all of the international guidelines recommended treatment beginning at CD4 counts of 350 (or were actively considering a standard of CD4 counts of 350) and NIH research had concluded that delaying initiation of treatment to 200-250 risked early death. Those subjects whose CD4 counts were allowed to drop to 200-250 (or to become symptomatic with AIDS) were needlessly allowed to progress to AIDS, impacting their mortality and disease complications while also needlessly increasing the risk of transmission of HIV infection to uninfected partners.

- Inadequate Informed Consent: The so-called informed consent document for this study was 19 pages long. It failed to inform the subject that he/she could receive HIV treatment below the standard of care (CD4 of 350) in their country or by international standards of care, and that the disease could be allowed to progress until the CD4 count fell to 200 before treatment was initiated, during which AIDS would occur and her/his partner could become infected. Further, the Brazilian participants were not informed that the standard of care in Brazil already was to treat at CD4 350; yet one of the Brazilian study groups received no treatment until their CD4 count had dropped to 200.

- Vulnerable Subjects: This study was carried on in Brazil, India, Thailand, Botswana, Kenya, Malawi, South Africa, and Zimbabwe. While we do not have the identity of the subjects, it is reasonable to assume that many were not capable of understanding the elaborate informed consent documents, that health care workers did not have the time to individually translate and counsel subjects, and that the subjects were poor and uniformed when it came to HIV treatment. They trusted that they were receiving appropriate care.

HPTN 046 http://www.hptn.org/research_studies/hptn046.asp

HPTN 046 was a study of prevention of mother to child HIV transmission (PMTCT). During the third trimester of pregnancy, HIV infected participants received HIV counseling and the intrapartum/neonatal two-dose NVP prophylaxis regimen to prevent transmission of HIV from mother to child. Infants were randomly assigned to one of two groups at Week 6 following birth to receive either extended NVP or placebo through the first 6 months of life or until cessation of breastfeeding, whichever occurred earlier. All mothers and infants outside of the study were offered the local standard of care antiretroviral (ARV) regimen for the prevention of MTCT, but these ARVs were not provided by the study.

- Deliberate withholding of treatment allowing HIV disease to progress for research purposes: HPTN 046 provided inferior treatment for HIV prevention and placed mothers and infants at risk for increased HIV infection. Mothers enrolled were provided with inferior treatment for their own HIV infection. Researchers allowed infected mothers to continue without treatment for their own infection, or initiated treatment at unacceptably low CD4 counts or at an advanced stage of disease, notwithstanding knowledge that treatment with highly active antiretroviral treatment (HAART) during pregnancy was more effective at preventing HIV transmission to infants and delaying the onset of AIDS in the mother. The research team informed the subjects only of results of studies of inferior treatment of infants which supported their study design. They withheld highly relevant and material information about the results of studies from countries that demonstrated a marked decrease in HIV transmission with HAART, and with continued treatment during breast feeding. In addition, the research team failed to communicate the benefits of early treatment of HIV infected individuals. These failures to disclose placed infants at risk for HIV infection and mothers at risk for unnecessary progression to AIDS.

- Selection of study locations and subjects to avoid stringent ethical oversight: HPTN 046 improperly utilized at-risk populations for clinical studies in nations with inferior standards of care allowing inferior treatment. The studies could not have been performed in the U.S. or other nations which imposed appropriate standards of care.

- Lack of accurate informed consent and failure of the Data and Safety Monitoring Board (DSMB) to insist on properly informing study subject of research advances: The DSMB of HPTN 046 did not properly revise the study to conform to results from other NIH and non NIH sponsored studies of PMTCT treatment of HIV-infected adults and children. By thus allowing inferior treatment and prevention to continue, the research team placed study participants at risk for HIV infection and disease progression. The informed consent document was overly complex. It is highly doubtful that it could have been properly communicated or understood by the majority of study participants.

- Failure to inform sexual partners of known HIV infected study participants that they were likely to be infected and require treatment. No evidence exists that counseling of research study participants included explanation of the importance of informing their sexual partners that they might have become infected and could benefit from treatment.

- Lack of community participation and potential conflict of interest: Noticeably absent was any evidence of community advocates or expert review by non-conflicted individuals. There were no community representatives or patient advocates listed as advisers to the clinical trial.

Summary:

Having reviewed publications on the Guatemala study, the Tuskegee experiment and selected U.S. Government-sponsored clinical research studies in resource-poor countries, we cannot escape the conclusion that the studies share a common thread of violation of international ethical principles related to research in human subjects. These violations include the utilization of vulnerable subjects without adequate protection from irreversible harm, inadequate warning of risks of involvement in research, and denial of treatment or delays in treatment which resulted in significant harm to the health and welfare of research subjects. We urge the Commission to closely examine all current NIH-sponsored studies and procedures for protecting vulnerable human research subject in resource-poor countries and to recommend measures to prevent future violations of ethical principles.

It is our opinion that the common precipitating ethical principle that was violated and links the Tuskegee, Guatemala and recently NIH sponsored studies is:

It is unethical to perform clinical research on vulnerable subjects when the internationally recognized standard of care is not provided, to delay or deny that standard of care treatment where such actions may increase the risk of harm to the subjects, and to fail to fully inform the subjects in an easily comprehensible manner of the nature, personal risks, possible consequences of their participation and of research study advances that may affect their continued participation in the research study.

Submitted to the Presidential Commission for the Study of Bioethical Issues

Global Strategies for HIV Prevention

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