From the Instructor

In WR 150 we explore the history of human subject protection in health research, beginning with the infamous Tuskegee Study of Untreated Syphilis. The revelation of this 40-year non-therapeutic study of 400 African American sharecroppers prompted a critically needed overhaul of federal guidelines for health research. These reforms, however, do not extend to health studies conducted outside the United States, prompting some bioethicists to charge that clinical trials undertaken in developing countries, where there is poor or absent medical care, constitute the new "Tuskegee." Kim Clark tackles these assertions by positioning the Tuskegee study as the reference point for an examination of such research, refuting the charge of exploitation and, further, identifying research benefits.

— Melanie Clark

From the Writer

I began researching my paper "Clinical Trials in Developing Countries: The New 'Tuskegee?'" with the mindset that my thesis would be an affirmative answer to the question. However, I discovered that, despite my personal opinion, sources were pushing me in the opposite direction. Although I usually do not write a paper with a thesis that I do not agree with, I saw this paper as an opportunity to strengthen my persuasive writing skills. Because I was skeptical, I noticed flaws in my argument that I might not have anticipated if I had been already convinced of my viewpoint. As a result, my paper has the most convincing argument that I have ever written.

— Kimberly Clark

Kimberly Clark

Clinical Trials in Developing Countries: The New "Tuskegee"?

Imagine the suffering that a West African HIV-positive pregnant woman endures as she grapples with the heartbreaking possibility that she might pass the HIV virus to her unborn child. Her situation appears hopeless; she lives in a developing country where the rates of HIV are high and the quality of medical care is low. Now imagine that researchers from the United States tell her that they have a drug, called zidovudine, which could protect her baby from HIV. When asked if she would give her consent to participate in a placebo-controlled clinical trial testing the efficacy of the drug, what will she decide? For Nicole, living in the Ivory Coast, pregnant and HIV-positive, her choice was simple: "As long as there was a possibility to save my daughter, I had to try" (qtd. in French). Nicole was not alone in her decision; she was one of thousands of women, all desperately trying to save the lives of their unborn children, who participated in placebo-controlled trials testing zidovudine held throughout developing countries. However, controversy soon swirled around the trials. Outraged by the chance that the study participants received a placebo rather than the drug that was proven effective in earlier trials (Sperling 1621–1622), many people claim that the women were being exploited. One of such critics, Marcia Angell, as the executive editor of the *New England Journal of Public Health*, claims that the trials demonstrated that research "[has] not come very far from Tuskegee" (849). Indeed, the possibility that a woman like Nicole received a placebo in lieu of the drug with proven potential to save the health of her child evokes the ordeals of the syphilitic African American men from whom treatment was purposefully withheld during the Tuskegee Study of Untreated Syphilis

(TSUS). Why then, were the trials allowed to continue if they were indeed exploitative? The type of exploitation found in the HIV trials was considered non-harmful since it involved researchers rather than doctors and considerable benefits to the study population. Therefore, despite their similarities, the HIV placebo-controlled trials were justified while the TSUS was not.

A direct comparison of the TSUS and the trials in question is legitimate to a point. Both were research studies that involved a vulnerable population afflicted with a life-threatening disease, an adherence to the local standard of care, and the intention to withhold treatment despite its proven efficacy. For the TSUS, the vulnerable population was poor African American men; the disease was syphilis; the justification for withholding the treatment was that the men were never going to receive medical care anyway (Brandt 18). Despite living seemingly worlds away, the HIV-positive women participants of the placebo-controlled trials shared quite a bit with the men of Tuskegee. They were seriously sick, living in an economically disadvantaged country where living with health care was the exception and living without it was the norm. The fifty percent chance that they received a placebo and would continue to live without the drug that could save the health of their children results from the fact that the local standard of care in developing countries offers no treatment (World Health Organization). Both situations involved a study population in deplorable conditions and authoritative study leaders with the ability to take advantage of such conditions; the TSUS involved white doctors and poor black men and the placebo-controlled trials involved U.S. researchers and women of developing countries. In light of these similarities, the main connection between the TSUS and the HIV placebo-controlled trials can be determined as exploitation. However, exploitation remains both the common thread and the dividing factor of the TSUS and the HIV placebo-controlled trials.

Such a division occurs because, although both the TSUS and the HIV placebo-controlled trials involved exploitation, ethicists consider a certain type of exploitation to be ethical. While the common definition of exploitation pertains to the concept of the first person taking an unfair advantage of the second person so that the first person benefits, Jennifer S. Hawkins, an ethicist and associate research professor at Duke

University, elaborates on that definition by explaining that exploitative actions are characterized by "*procedural* and *outcome* unfairness" (Hawkins 251). Procedural unfairness deals with the way in which an incident commenced, occurring when, for example, a research study gains participants through questionable means such as deception, coercion or uninformed consent (Hawkins 251). Outcome unfairness quite understandably deals with an unjust result of a study which occurred due to "*harmful* . . . [or] . . . *nonharmful* (though still unfair) transactions" (Hawkins 251).

Hawkins defines harm as an instance in which the outcome of the study "lowers [the participants'] significant interests or sets them back relative to where they would have been otherwise" (Hawkins 253). However, Hawkins notes that "there is controversy over whether this is the only baseline that counts" as "[s]ometimes *omissions* seem like harms" (254). Some people consider that allowing a person to suffer from a disease simply because it is a common occurrence, or baseline, where they live constitutes harm. Hawkins describes such omissions, in which a person "has a preexisting moral obligation to aid [another person] but fails to do so" as "cases of *positive obligation flouting*" (254). Whether or not positive obligation flouting causes harm depends on the particular obligations one person owes to another. For instance, a doctor's refusal to treat her patient epitomizes an unethical action; the doctor causes harm through the positive obligation flouting of the established obligation doctors have to treat their patients (Hawkins 257). However, since "[h]ealing is not internal to the special goals of research" (Hawkins 262), researchers must fulfill a different role than doctors and therefore must have different obligations. Hawkins defines such obligations as "*Good Samaritan obligation*[s]" which "everyone has simply in virtue of being a moral agent" (257). However, unlike the obligations of doctors, Good Samaritan obligations cannot be enforced. For placebo-controlled studies, there are three conditions which warrant a researcher to flout his or her Good Samaritan obligation. The conditions indicate that "the aim of the research must be morally weighty . . . a placebo-controlled trial must be the *only* way to obtain the information in question . . . [and] . . . the community from which the subjects will be drawn must be one that could greatly benefit, and is also reasonably likely to benefit, from the research"

(Hawkins 273). Therefore, if a trial meets all three conditions, the researchers can ethically flout their obligations to aid the study subjects by administering placebos.

The exploitation in the TSUS and the HIV placebo-controlled trials demonstrated that while the TSUS was unethical due to its harmful outcome, the circumstances of the HIV trials warranted the use of placebos. The TSUS clearly denoted procedural unfairness since the doctors led the men to believe that they had received treatment (Jones 119) and encouraged the men's participation through incentives, such as payment for a proper burial (Brandt 25). In contrast, numerous reviewers scrutinized the study designs of the HIV placebo-controlled trials to ensure that the trials aligned with ethical standards (Dept. of Health and Human Services) thus eliminating any procedural unfairness.

On the other hand, outcome unfairness was undoubtedly present in the TSUS and the HIV placebo-controlled studies since the designs of the studies denied treatment to all of the Tuskegee men and some of the HIV-positive women. The outcome unfairness of the TSUS resulted in harm since the study leaders presented themselves as doctors to the men without the intention to actually treat the men. However, because the HIV trials involved researchers, the administration of placebos was not automatically unethical. Furthermore, the trials met the three general conditions which warrant a researcher to flout his or her Good Samaritan obligation to treat a sick study participant. The need for the trials was greatly demonstrated by the fact that, as Ivory Coast doctor Rene Anatole Ehounou Ekpini noted, "the alternative [to the placebo-controlled trials] is giving everyone here the placebo treatment, because if you step outside, that is what pregnant women with the disease are getting here: nothing" (qtd. in French). Upon reviewing the study designs for HIV drug trials, the World Health Organization asserts that "placebo-controlled trials offer the best option for obtaining rapid and scientifically valid results" (World Health Organization). Also, since the objective of the trials was "the exploration of alternative regimens that could be used in the developing world" (World Health Organization), the women of the developing countries stood to gain enormous benefits from the trials "as there [was] currently no effective alternative for HIV-infected pregnant women [in those parts of the world]" (World Health Organization). Therefore, the use of the placebos,

although exploitative, was not unethical since the particular circumstances authorized the researchers to flout their obligations.

Critics of the HIV placebo-controlled trials maintain that the use of placebos was not warranted by the HIV trials nor were they ethically sound to begin with. Many disagree that the local standard of care of no treatment in developing countries justified the use of placebos. Indeed, the placebo control groups raised ethical implications, especially in light of the Declaration of Helsinki which states that "every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study" (Declaration of Helsinki). In addition, guidelines which state that "[t]he ethical standards applied [in the developing country] should be no less exacting than they would be in the case of research carried out in [the sponsoring] country" (Lurie 853) indicates that since the use of placebos in a United States HIV trial would be unethical since an effective treatment had been established (World Health Organization), the same applies to U.S.-led trials in developing countries.

Furthermore, many critics advance, and even some defenders acquiesce, the belief that a placebo-controlled study was not the only way to obtain the desired information (Lurie 854). For instance, an HIV trial for pregnant women in Thailand did not involve placebos since the study leaders asserted that a placebo control group would be unethical. However, a researcher involved acknowledges that "[a]dding a placebo arm to our study design could provide added reassurance that the [treatment] is as effective in the Thai population as in the original study and a more definite estimate of the degree of efficacy of the shortened regimen over no treatment" (Lie 190). In other words, while both critics and defenders indicate that a non-placebo HIV trial was indeed possible, they both recognize that a placebo-controlled trial provided the most reliable information and the quickest way to develop a drug applicable to the developing world. Despite the exploitation that resulted from the use of placebos, the placebo-controlled trials remained the most effective solution to the problem at hand.

While Nicole's story demonstrates her vulnerability to exploitation, it also establishes her opportunity, and the opportunity of her country, to gain from the trials despite the use of placebos. This is not to say that

a placebo-controlled study was the optimal solution to the problem. In an ideal situation, researchers would be able to give the HIV drug to every woman in desperate need of treatment. But such methods might be equated to placing a Band-Aid over a knife wound: a short-term solution for a long-term problem. Still, placebo-controlled trials are not warranted in every situation. The use of placebos in the HIV trials held in developing countries did not set a precedent for the use of placebos in future trials. However, the depth of the debate surrounding the trials and the thorough review of study designs did set an important precedent for future trials to follow. No longer are people satisfied with silence when they believe study participants are being exploited. No longer are researchers content with study designs that give results but inflict harm upon participants. The outspoken opposition of critics and the careful methods of researchers prove that the placebo-controlled HIV trials have indeed come very far from Tuskegee.

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KIMBERLY CLARK is a sophomore in the College of Arts and Sciences studying biological anthropology and public health. She plans to pursue a career in science communications. This essay was written for Melanie Smith's course, WR 150: Ethical Issues in Public Health.