Clinical research in third world countries

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It is common knowledge many clinical research activities have been carried out in developing countries with collaboration of research institutions from developed countries. It is equally important that the participants, research subjects and researchers from developing countries fully understand the real implications and benefits of the research. This article will attempt to explore the methods and outcomes of research done in developing countries and will focus on research done on HIV/AIDS and STIs.

The participants who take part in clinical research in third world countries have expectations. These significantly influence the behavior and experience of participants during the research. Common expectations of participants include that they will receive some care and health benefits, that personal information will be kept confidential, that they will be counselled regarding how to avoid HIV and STI infections or to live with HIV/AIDS. At the same time they expect that transportation and out-of-pocket expenses will be paid. Participants may also have unrealistic expectations of benefits, and little understanding of risks emanating from the research. In particular, the basis of randomized control trials may not be fully understood by participants. There is difficulty in explaining placebo controls to participants who expect that their participation will indeed benefit them. Furthermore, expectations are likely to differ depending on the source that created the expectations (eg. research staff, family, community, government officials), as well as on the level of knowledge and sophistication of the participant.

A few months before the 13th International Conference on AIDS held in June 2000 in Durban, South Africa, the following news appeared on a web page of HIV prevention.

“Dr. Thomas C. Quinn from Johns Hopkins University and his colleagues through their criminal negligence allowed 90 of their clinical trial participants to get HIV infected during their clinical trial in Uganda. They could have prevented these people getting HIV infected but to retain their study integrity they failed to inform the participants about the possibility of their being infected, which is criminal negligence and complete disregard for the life of people in Rakai District of Uganda”.

The author of the article was Joe Thomas, a HIV/AIDS prevention activist from Australia. He wrote under the heading of “Criminal negligence of Johns Hopkins University AIDS researchers”.

Commenting further Joe Thomas said “Considering the gravity of the situation, I would urge the AIDS activists to explore the possibility of a class action legal suit to force the researches and their sponsors to pay the punitive and compensatory damages to their study participants in Uganda”.

The following institutions were involved in this study:

1. The National Institution of Allergy and Infectious Disease, Bethesda, USA
2. Johns Hopkins University, Baltimore, USA
3. Columbia University, New York, USA
4. Faculty of Medicine, Makerere University, Kampala, Uganda

Grants for this study were awarded by National Institute of Child Health and Human Development, Rockefeller Foundation, and the World Bank. Some of the drugs and laboratory testing facilities were provided by Pfizer, Abbot Laboratories, Roche Molecular Systems, and Calypte Biomedical. The study was published in New England Journal of Medicine (NEJM)¹

Marcia Angell, the editor of the NEJM severely criticized this study as unethical in a strongly worded editorial in “Investigator’s responsibilities for human subjects in developing countries”². She queried that most people agree that investigators assume some responsibility for their human subjects but how much? And does it matter where the research is carried out?

The study was carried out in 10 clusters of rural villages in Uganda to delineate the risk factors associated with heterosexual transmission of the HIV-1. Villagers including pregnant women were surveyed on five occasions at 10-month intervals. The first goal of the project was to determine whether sexually transmitted diseases (STDs) such as syphilis and gonorrhea increase the risk of HIV infection. To study that question, the investigators gave residents of 5 of the 10 clusters intermittent antibiotic treatment to reduce the STDs. At each survey, villagers were asked about their sexual practices and medical histories, and blood and other body fluids were taken for testing for HIV-1 and STDs. As reported in a paper in the Lancet³, antibiotic treatment reduced the prevalence of their STDs, but not the incidence of HIV-1. An increasing viral load in the initially HIV-1 positive partner was associated with a greater risk of transmission. In addition circumcision was found to be protective in male partners.

It is important to be clear about what this study meant for the participants. It meant that up to 30 months, several

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hundred people with HIV infection were observed but not treated. It was also left up to the seropositive partner in couples discordant for HIV-1 to decide whether the seronegative partner would be informed even though the investigators regularly saw both. In addition, many people who were found to have other STDs were left to seek their own treatment. For example those who lived in the five village clusters given mass antibiotics also received immediate intramuscular penicillins, if they had a positive serological test for syphilis, but in the other, such people were simply referred to free government clinics. Such a study could not have been performed in the United States, where it would be expected that patients with HIV and other STDs would be treated. In addition in most states it would be expected that caregivers would see that seronegative partners were informed of their special risk⁴.

The former Director of the Centers for Disease Control and Prevention (CDC) and later Surgeon General, David Satcher and Director of the National Institutes of Health (NIH), Harold Varmus commented on the same study in NEJM⁵. After the Tuskegee study was made public in the 1970s a national commission was established to develop principles and guidelines for the protection of research subjects. The new system of protection was described in the Belmont report⁶ although largely compatible with the World Medical Associations' Declaration of Helsinki⁷.

The Belmont report articulated three principles: respect for persons (the recognition of the right of persons to exercise autonomy), beneficence (the minimization of risk incurred by research subjects and the maximization of benefits to them and to others), and justice (the principle that therapeutic investigations should not unduly involve persons from groups unlikely to benefit from subsequent applications of the research).

The chiefs of the CDC and the NIH continued to ask about how should these principles be applied to research conducted in developing countries? Such research must be developed in consultation with the developing countries in which it will be conducted. In the case of the NIH and CDC trials, there has been strong and consistent support and involvement of the scientific and public health communities in the host countries, with local as well as United States-based scientific and ethical reviews and the same requirements for informed consent that would exist if the work were performed in the United States. Interventions that would be expected to be made available in the United States might be well beyond the financial resources of a developing country or exceed the capacity of its health care infrastructure. These authors agree that the scientific and ethical issues concerning studies in developing countries are complex. It is a healthy sign that they are debating these issues so that we can continue to address our knowledge and our practice. However, they believe the debate should take

place with a full understanding of the nature of the science, the interventions in question, and the local factors that impede or support research and its benefits.

In the United States, three studies of clinical practice report that the AIDS Clinical Trial Group (ACTG) 076 regimen is associated with decrease of 50% or more in perinatal HIV transmission⁸⁻¹⁰. Peter Lurie and Sidney M. Wolfe attached to Public Citizen's Health Research Group, Washington DC, quoted an unpublished report of World Health Organization (WHO)⁹. The WHO group which included no ethicists, concluded "placebo controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent perinatal transmission of HIV". This unpublished document has been widely cited as justification for subsequent trials in developing countries. These authors strongly believe most of these trials are unethical and will lead to hundreds of preventable HIV infections in infants. They have found out primarily on the basis of documents obtained from the Centers for Disease Control and Prevention that 18 randomized controlled trials of interventions to prevent perinatal HIV transmission that either began to enroll patients after the ACTG 076 study was completed or have not yet begun to enroll patients.

The studies were designed to evaluate a variety of interventions: antiretroviral drugs such as zidovudine (usually in regimens that are less expensive or complex than the ACTG 076 regimen), vitamin A and its derivatives, intrapartum vaginal washing, and HIV immune globulin, a form of immunotherapy. These trials involve a total of more than 17,000 women.

In the two studies being performed in the United States, the patients in all the study groups have unrestricted access to zidovudine or other antiretroviral drugs. In 15 of the 16 trials in developing countries, however, some or all of the patients are not provided with antiretroviral drugs. Nine of the 15 studies being conducted outside the United States are funded by the U.S. government through the CDC or the National Institutes of Health (NIH), 5 are funded by other governments, and 1 is funded by the United Nations AIDS Program. The studies are being conducted in Ivory Coats, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic. These 15 studies clearly violate recent guidelines designed specifically to address ethical issues pertaining to studies in developing countries. According to these guidelines, "The ethical standards applied should be no less exacting than they would be in the case of research carried out in the sponsoring country"¹¹. In addition, US regulations governing studies performed with federal funds domestically or abroad specify that research procedures must not unnecessarily expose subjects to risk¹².

Taking into consideration of these facts which are very complex in nature in conducting research with the scientists in the developed countries, the researchers in this part of the world should obtain ethical clearance from all institutions which are involved in the research.

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Knowledge on HIV/AIDS among a group of selected workers from the hospitality, plantation, and industrial sectors

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Introduction

The estimated HIV prevalence rate in Sri Lanka is less than 0.1%. Sri Lanka is categorized as a country with a low HIV prevalence. Yet, there are certain socio-demographic and behavioural factors which may accelerate this rate. The National STD/AIDS Control Programme has identified certain behaviours such as multiple partners, frequent change of partners, low condom use, buying and selling sex as risk factors for the spread of sexually transmitted infections including HIV. The main mode of spread of HIV infection in the country is through unprotected sex. Hence the objective of preventive programmes should be to educate people on the behaviours that make them vulnerable to infection in order to facilitate changing such risky behaviours. Further HIV/AIDS has created a fear among people which has resulted in stigmatizing of and discriminating against

those infected. This may be because of misinformation or ignorance of basic facts about the disease. Therefore this study was planned to assess the knowledge on basic facts on HIV/AIDS among workers in three different working environments.

Methodology

This descriptive cross sectional study was carried out among 300 randomly selected workers in three work sectors. Two workplaces each from hotel, plantation and manufacturing sectors were selected randomly for the survey. The names of workplaces are withheld for purpose of confidentiality but the geographical location is given below. The pay roll of workers was used as the sampling frame and 50 respondents from each workplace was selected randomly using the systematic sampling technique.

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