HIV VACCINE TRIAL PARTICIPATION IN THE THIRD WORLD: AN ETHICAL ASSESSMENT.

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DECLARATION

I, the undersigned, hereby declare that the work contained in this assignment is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

SUMMARY

This essay examines the issue of trial participation in the proposed HIV Vaccine Trials in South Africa. It is set against the backdrop of ethical issues relating to research in the Third World in general.

Trial participation is examined in the context of the ethical tension that exists between international ethical research standards based on Liberal Individualism and local standards of care and cultural norms in the Third World. Two areas of conflict are inherent here: universality versus particularity on the one hand and individualism versus communitarianism, on the other.

The Tuskegee Syphilis Study as well as the HIV Vertical Transmission Trials are used as a point of departure to set the stage for the controversy surrounding the proposed HIV Vaccine Trials.

The important concepts of informed consent, the risk-benefit ratio and fair treatment of trial participants are framed within the Four Principle Approach of autonomy, beneficence, non-maleficence and justice. These principles form the cornerstone of the Declaration of Helsinki. This Western ethical guideline – grounded in universality – has become the mantra of all liberal democracies the world over and is chanted slavishly by the international research community. It bears the hallmark of liberal individualism with its mandate that "the concern for the interest of the individual must always prevail over the interests of science and society". Followed to its logical conclusion, any infringements of the moral interests of trial participants must be viewed using a subject-oriented approach. Such an approach sees the trial participant as being of paramount importance and views research as "highly desirable but morally optional".

Clearly, this would mean the end of the road for medical research, especially in the Third World, where a truly subject oriented approach would render research tantamount to exploitation of vulnerable, educationally disadvantaged persons.

In Africa, in traditional, rural communities, a moderate form of communitarianism referred to as "Ubuntu" or "communalism" is still prevalent. In such communities, the concept of personhood is embedded in the community or society. In these communities, a balancing approach, in which infringements on the rights of trial participants are permissible in the name of science or society, provided the subject is not placed at significant risk, would be acceptable. However, liberal individualism is making inroads here too. As such, the ethical tension between liberal individualism and communitarianism, which is unavoidable in research settings, is growing.

This essay highlights many internal contradictions in liberal individualism – especially where research ethics is concerned in Third World countries. One of the outcomes of such contradiction is the attempt by the World Medical Association to amend the Declaration of Helsinki – in the name of ethical relativism: different standards for different countries or cultures.

Surely, such liberal individualism cannot be seen as the "endpoint of mankind's ideological evolution" as Fukuyama phrases it, nor can it be the final solution to the problems of the world and, as such, "the end of history".

In the context of the HIV Vaccine Trials, individual good clashes with societal good, universality with particularity and ultimately, modernism with postmodernism.

In Western cultures, the individual enjoys priority; in other cultures, society is more important – somewhere in between, we need to find common ground which can be incorporated into a balancing approach with minimal risk to the individual when infringement of rights is unavoidable.

OPSOMMING

Hierdie werkstuk ondersoek die kwessie van deelname aan die voorgestelde kliniese HIV Entstof-proewe in Suid-Afrika. Die ondersoek geskied teen die agtergrond van die etiese kwessies wat opgeroep word deur navorsing in die Derde Wêreld in die algemeen.

Deelname aan hierdie kliniese proewe word ondersoek binne die konteks van die etiese spanning way bestaan tussen internasionale navorsingstandaarde, wat gebaseer is op liberale individualisme aan die een kant, en die standaarde van sorg en kulturele norme in die Derde Wêreld, aan die ander kant. Twee konflikareas is inherent aan hierdie spanning: enersyds universaliteit versus partikulariteit en andersyds individualisme versus kommunitarisme.

Die Tuskegee Sifilis Studie en die HIV Vertikale Oordragproewe word gebruik as 'n vertrekpunt om die kontroversie rondom die voorgestelde HIV Entstofproewe te bespreek.

Die belangrike konsepte van ingeligte toestemming, die risiko-voordeel ratio en die regverdige behandeling van deelnemers aan die proewe word bespreek binne die Vier Beginsel Benadering van outonomiteit, die plig om goed te doen ("beneficence"), die plig om nie kwaad te doen nie ("non-maleficence") en regverdigheid. Hierdie beginsels vorm die hoeksteen vir die Verklaring van Helsinki. Hierdie Westerse etiese riglyne, wat gegrond is in universaliteit, het die mantra geword van alle liberale demokrasieë die wêreld oor en word slaafs nagevolg deur die internasionale navorsingsgemeenskap. Dit dra die stempel van liberale individualisme met sy mandaat dat "die belang van die individu altyd moet voorkeur geniet bo die belange van wetenskap en die samelewing". Die logiese konklusie van hierdie argument is dat enige beperking op die morele belange van die deelnemers aan hierdie proewe, beskou moet word in die lig van 'n subjek-georiënteerde benadering. So 'n benadering beskou die proewe-deelnemers as van kardinale belang en sien navorsing as "hoogs wenslik, maar moreel opsioneel".

Dit impliseer egter die einde van mediese navorsing, veral in die Derde Wêreld, aangesien 'n ware subjek-georiënteerde benadering sal veroorsaak dat navorsing neerkom op die uitbuiting van kwesbare, opvoedkundig benadeelde persone.

In Afrika kom 'n gemagtigde vorm van kommunitarisme, wat beskryf word as "ubuntu" of "plaaslike selfbestuur" ("*communalism*") steeds voor in tradisionele, landelike gemeenskappe. In sulke gemeenskappe is die konsep van persoonsyn ingebed in die gemeenskap of samelewing. In hierdie gemeenskappe is 'n meer gebalanseerde benadering eerder gewens, dit wil sê, 'n benadering waar skendings van die regte van proewe-deelnemers toelaatbaar is is die naam van die wetenskap of die samelweing toelaatbaar is, mits die subjek nie in 'n te groot gevaar geplaas word nie. Liberale individualisme begin egter ook hier 'n toenemende invloed uit te oefen. Die etiese spanning tussen liberale individualisme en kommmunitarisme, wat onafwendbaar is in 'n navorsingsomgewing, word in werklikheid al hoe groter.

Hierdie werkstuk wys op talle interne teenstrydighede wat voorkom in liberale individualisme, veral ten opsigte van navorsingsetiek in die Derde Wêreld. Een van die gevolge van so 'n teenstrydigheid, is die poging deur die Wêreld Mediese Vereniging om die Verklaring van Helsinki te wysig in die naam van etiese relativisme en te vra vir verskillende standaarde vir verskillende lande en kulture.

Sekerlik kan sodanige liberale individualisme nie beskou word as die "*endpoint of mankind's ideological evolution*", soos Fukuyama dit stel nie ook nie as die finale oplossing van die wêreld se probleme en as sodanig die "einde van geskiedenis" nie.

In die konteks van die HIV Entstofproewe, is daar 'n botsing tussen dit wat goed is vir die individu en dit wat goed is vir die samelewing, tussen universaliteit en particulariteit en uiteindelik tussen universaliteit en partikulariteit en uiteindelik tussen modernisme en postmodernisme.

In die Westerse kultuur geniet die individu die hoogste prioriteit, maar in ander kulture is die samelewing belangriker. Dit is egter nodig dat ons iewers in die middel 'n gedeelde grondslag vind wat gëinkorporeer kan word in 'n meer gebalanseerde benadering, met minimale risiko vir die individu, veral in die gevalle waar en wanneer dit onvermydelik is om inbraak te maak op indiviuele regte.

DEDICATION

I would like to dedicate this thesis to my husband, Premesh and our sons, Kehar and Nikhal whose love and support sustained me through some of the most trying moments in the preparation of this document.

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ABSTRACT

Set in the context of ethical issues relating to research in the Third World, this paper examines the thorny issue of trial participation in the proposed HIV Vaccine Trials in South Africa. Such participation is viewed against the backdrop of the ethical tension that exists between international ethical standards based on Liberal Individualism and local standards of care and cultural norms in the Third World. Conflict exists between universality and particularity, on the one hand, and between individualism and communitarianism on the other.

The Tuskegee Syphilis Study as well as the HIV Vertical Transmission Trials are used as a point of departure to set the stage for the controversy surrounding the proposed HIV Vaccine Trials.

The important concepts of informed consent, the risk-benefit ratio and fair treatment of trial participants are framed within the Four Principle Approach of autonomy, beneficence, non-maleficence and justice - which forms the cornerstone of the Declaration of Helsinki. This Western ethical guideline – grounded in universality – has become the mantra of all liberal democracies the world over and is chanted slavishly by the international research community. With its mandate that the "concern for the interest of the individual must always prevail over the interests of science and society", it bears the hallmark of liberal individualism. Followed to its logical conclusion, any infringements of the moral interests of trial participants must be viewed using a subject-oriented approach. Such an approach sees the trial participant as being of paramount importance and sees research as "highly desirable but morally optional".

Clearly, this would mean the end of the road for medical research, especially in the Third World, where a truly subject oriented approach would render research tantamount to exploitation of vulnerable, educationally disadvantaged persons.

In Africa, in traditional, rural communities, a moderate form of communitarianism referred to as "Ubuntu" or "communalism" is still prevalent. In such communities, the

concept of personhood is embedded in the community or society. A balancing approach, in which infringements on the rights of trial participants are permissible in the name of science or society, provided the subject is not placed at significant risk, would be acceptable in these communities. However, liberal individualism is making inroads here too. As such, the ethical tension between liberal individualism and communitarianism, which is unavoidable in research settings, is growing.

This essay highlights many internal contradictions in liberal individualism – especially where research ethics is concerned in the setting of Third World countries. One of the outcomes of such contradiction is the attempt by the World Medical Association to amend the Declaration of Helsinki – in the name of ethical relativism: different standards for different countries or cultures.

Surely, such liberal individualism cannot be seen as the "endpoint of mankind's ideological evolution" as Fukuyama phrases it, nor can it be the final solution to the problems of the world and as such, "the end of history".

In the context of the HIV Vaccine Trials, individual good clashes with societal good, universality with particularity and ultimately, modernism with postmodernism.
In Western cultures, the individual enjoys priority; in other cultures, society is more important - somewhere in between, we need to find common ground which can be incorporated into a balancing approach with minimal risk to the individual when infringement of rights is unavoidable.

HIV Vaccine Trial Participation in the Third World – An Ethical Assessment.

INTRODUCTION

With 16000 new people infected daily throughout the world, HIV/AIDS is increasingly being recognised as an illness of **global importance** and is regarded as a major priority for the **world community.** It is generally accepted that an effective preventive HIV vaccine could be a powerful tool in the struggle against the expanding HIV pandemic. However, such a vaccine would have to be tested in clinical trials using human subjects in the absence of a suitable animal model.

Recruiting volunteers for these trials is critical to the success of the endeavour, yet it is fraught with scientific, social, political and ethical concerns – especially when the target communities live in the Third World.

Possible host community responses range from "opposition and obstruction, to indifference, support or active participation" (Hodel 1994: 255).

For individual participants, a wide range of factors might influence a decision to participate – concerns about adverse reactions, anxiety about the possibility of being infected by the vaccine and a host of "social harms" like discrimination by friends, family, employers, life or health insurance companies, blood banks and restriction on international travel (Hodel 1994: 255).

Thus, to achieve truly informed consent, it is critical to determine what information is to be given to potential volunteers in order for them to make an informed decision. A vital component of such patient information is the risk-benefit ratio that determines the ethical acceptability of clinical research. In AIDS vaccine research, however, the half of the equation that deals with risk is "virtually unknown". There is no data about the potential for risks such as "vaccine-induced immunotoxicity or antibody-induced enhancement of infection" (Tacket and Edelman 1990:356).

There is also no guarantee that those participants who do become infected during the trial will receive expensive anti-retroviral treatment that is not the standard of care in most developing countries.

It is thus evident that the proposed HIV vaccine trials in the developing world will be inundated with ethical concerns.

In anticipation of the launch of HIV vaccine trials worldwide, guidelines have been developed to ensure that " ethical issues **do not impede** the development of a new vaccine"! (United Nations Programme on AIDS - UNAIDS).

These ethical guidelines are designed to protect the **rights** of those participating in international vaccine trials and are based on the Helsinki Declaration of 1975, which mandates that "concern for the interest of the individual must always prevail over the interests of science and society". As such the issues central to this endeavour include, inter alia, **individual informed consent**, obligations of trial sponsors to host countries to provide vaccines, if they prove to be effective, and the use of expensive antiretroviral treatment for participants in developing countries who become infected during the trials.

In keeping with the ethos of the host country – the United States – the ideal of liberal individualism reigns supreme. The emphasis has clearly and strategically been placed on the protection of the rights of trial participants. Informed consent is detailed as follows - participants must be given a subject information sheet, a third party advisor must be accessible, participants should have time to reflect on their decisions and then give written informed consent.

In reality, however, the issue of obtaining informed consent from trial participants in developing countries is frightening! How does one explain the intricacies of randomised placebo controlled vaccine trials to vulnerable, poorly educated, deprived individuals who barely understand the concept of a "virus" let alone a "vaccine".

In spite of this, investigators believe that "one cannot allow our inability to solve these problems to slow the progress of clinical trials - we need to recognise the complexity and respect norms while still proceeding with trials"! (Ron Bayer - HIV Centre, New York, 1998).

It does not seem to occur to such investigators that one cannot **proceed** with these trials without informed consent. Vaccine development must proceed but certainly not efficacy trials if important ethical issues are not resolved.

The paradox inherent in this endeavour involves the high priority placed on **the individual** and the rights of the individual, to achieve, ultimately, not only societal good but **global good.**
How do we ask the individual to simultaneously evaluate the process of informed consent, to reflect on a trial in which s/he is to be exposed to risks of unknown magnitude and vaccines of doubtful benefit - and make a decision to best protect him/herself - in a scientific research trial which, historically, involves the use of human subjects to enhance the general welfare of society?

The ethical dilemma central to this essay revolves around individual good as opposed to societal good - stated in established Western terms. Does this dilemma or this distinction even exist in the Third World, in general, and in South Africa, in particular? In spite of the fact that 10% of the world's HIV infection occurs in South Africa, what value is attached to individual good or societal good in a community entrenched in an ethos of fatalism where the threat to life posed by HIV is no greater than the threat to life which exists on a daily basis?

On a deeper philosophical level, what will be the outcome of the wave of liberal individualism that is spreading rapidly across the world? The burgeoning human rights culture that has taken root across the globe has many ardent supporters, even in cultures where communitarianism is valued in some form or another. On the African Continent, and in South Africa, in particular, we are familiar with the concept of "Ubuntu" – " I am because we are". This concept favours communal values over Western individualism. In fact, the individual exists only in the context of the community. However, even these communities have been influenced by the Western ideals of individualism and materialism.

Are we now going to ask the people of Africa, who are not necessarily in agreement with Western concepts, to first and foremost consider their individual rights and then give informed consent to participate in vaccine trials which will benefit all of humankind? My fear is that they may have consented, on altruistic grounds alone, at an earlier place in

time. However, now, given the risks to themselves as individuals, will they still consent without a material inducement they have been taught to value by the West?
A study conducted in Thailand amongst potential volunteers in a phase 1 HIV vaccine trial to explore their motivations for participation in these trials found that personal benefit as opposed to altruistic motives were important (Jenkins 1995: 36-42).
This finding was echoed in another study that looked at willingness of high-risk populations to participate in AIDS vaccine trials in Thailand. This study found that "the principal inducement to join a trial was health insurance" (Celentano1995: 1079-1083).
Yet another study, also conducted in Thailand, to look at Hepatitus B Immunization as a potential incentive for trial participation, concludes that "concrete health benefits may offer the most compelling incentives to volunteers" (Beyrer 1996:399).
Undoubtedly, the search for incentives has begun!
If this occurs, if some form of manipulation is employed to ensure participation, where is the element of voluntariness in the informed consent thus obtained ? Can ethical trials be conducted in this fashion?

This essay examines the issue of trial participation in proposed HIV vaccine trials in South Africa against the backdrop of the ethical tension that exists between international ethical standards based on Liberal Individualism and local standards of care and cultural norms in the Third World. Many of the principles of African "Communitarianism" or Ubuntu, which exists in various forms especially in rural, traditional South African communities, are in stark contrast to the individualistic principles of the West. Yet, the individualism of the West has influenced African cultures to a significant degree. Our Constitution and Bill of Rights bear testimony to this. As a result, it is no longer easy for Western countries to engage in research in Africa without respecting the culture of human rights which has developed here. This change in emphasis from the community to the individual has started to influence research opportunities and possibilities in the Third World. Fulfilling all the criteria of international guidelines for the performance of ethical research in the Third World is starting to become problematic. How will the West respond? Will ethical relativism become a viable option and a convenient solution?

In order to place the ethical concerns of the HIV vaccine trials in perspective, the historical Tuskegee Syphilis Study will be used as a point of departure. The Vertical Transmission of HIV Trials will be briefly revisited to highlight the attention being focused on research ethics in the Third World. The classical "Four Principles" approach will then be examined to explore ethical concerns central to the HIV vaccine trials and its relevance in the African context will be discussed.

Limitations on the individual's moral interests will be explored using three possible moral frameworks – the societal view, the subject-oriented approach and a balancing approach - with an interplay between the benefits of the subject and society.

Ultimately, the idea that an appeal to "Ubuntu" might be our only hope of conducting ethical HIV vaccine trials in South Africa will be explored. However, will this retreat to ethical relativism be acceptable to the people of Africa?

3. RESEARCH ETHICS IN DEVELOPING COMMUNITIES

3.1 Introduction

Developing communities around the world are seen as excellent candidates for medical research largely because of the unfortunate but typical characteristics of these communities – they tend to be over-populated, poor, malnourished, illiterate and desperate. Under these conditions, together with a fragile health-care infrastructure, diseases thrive, especially infectious diseases. Under these conditions, empirical scientific research also thrives – statistically significant data can be obtained from large- scale clinical trials on thousands of human "volunteers".

As a result of this,

" Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country."

Lurie and Wolfe - 1997

Public Citizen's Health Research Group

These sentiments were expressed in the *New England Journal of Medicine* in September 1997 when a heated debate was sparked by trials in the developing world on HIV infected pregnant women to assess if short-course anti-retroviral treatment could reduce the transmission of HIV from mother to child. The ethical concerns raised by these trials were seen by some members of the medical profession as reminiscent of ethical concerns raised many years earlier by the Tuskegee Study.

3.2 The Tuskegee Syphilis Study

This study has been described as the longest running "nontherapeutic experiment" on human beings in medical history and "the most notorious case of prolonged and knowing violation of subject's rights" (Caplan 1992: 29).

The Tuskegee Study of Untreated Syphilis was sponsored by the United States Public Health Service. The study began in 1932 and continued till 1972. Over this 40 year period of human experimentation, 412 African-American men with untreated Syphilis were observed and compared with 204 men who were free of disease to determine the natural history of syphilis. When the study began, there was no good treatment available except for heavy metals, which were the standard of treatment. However, "the research continued even after penicillin became widely available and was known to be highly effective against syphilis". The study continued until it was brought to the attention of a reporter. The "outrage provoked by front-page stories in the *Washington Star* and the *New York Times* embarrassed the Nixon administration into calling a halt to it"(Angell 1997: 847-849).

The ethical violations here occurred not in a developing country outside the United States, but rather in a disadvantaged "developing" community inside the developed First World continent.

According to Marcia Angell in an editorial in the *New England Journal of Medicine* of September 1997," the ethical violations were multiple: subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment; and the study was continued even after highly effective treatment became available".

A special article in the *Hastings Centre Report* in 1992 confirms that subjects were recruited with misleading promises of "special free treatment" which, in reality, consisted of spinal taps done without anaesthesia to study the neurological effects of syphilis.

An article in the *New York Times* published on the 26 July 1972 describes the various incentives which were used to ensure trial participation - " free transportation to and from

hospitals, free hot lunches, free medicine for any disease other than syphilis and free burial after autopsies were performed".
The ethical violations inherent in the Tuskegee study were clearly in contravention of the Declaration of Helsinki (1964) which states that " the interests of the subject must always prevail over the interests of science and society"(Gillon 1986: 11).

On the other hand, the researchers involved in the Tuskegee study argued that the African-American men in the study probably would not have been treated anyway, so investigators were "merely observing what would have happened if there was no study". The study itself was regarded as important, a " never- to- be- repeated opportunity", especially after Penicillin became available.
In order to see the paralells in research subsequently conducted in the Third World, it is necessary to look at the HIV Vertical Transmission Trials.

3.3 HIV Vertical Transmission Trials In Pregnant Women

In 1994, the results of the first randomised placebo controlled study on pregnant women infected with HIV were published. It was established that treatment of these women with the antiretroviral drug Zidovudine during pregnancy and delivery reduced the transmission of the virus from mother to child by 67%. From this point onwards, Zidovudine became the best proven standard of treatment for all HIV infected pregnant women in the United States (Connor,et al 1994:1173-1179).
The drug regime used in this landmark study is, however, very expensive and totally unaffordable to Third World countries. The next logical step was therefore to investigate the possibility of shorter and hence cheaper courses of treatment. As a result, 16 trials were launched in developing countries around the world. 15 of these 16 trials were randomized and placebo controlled. HIV infected pregnant women in the study group were given a short course of Zidovudine and the incidence of transmission of the virus to their babies was established. However, the pregnant women in the control group were given a placebo. And, this is where the controversy began (Lurie and Wolfe 1997: 853).

In order to understand the context of the debate, it is essential to look briefly at the basic ethical principles of randomised clinical trials. It is an essential pre-requisite that when a randomised clinical trial compares two different treatments for a disease that there should be no good reason for thinking that one is better than the other. Hence, investigators need to be in this state of clinical "equipoise" when embarking on a randomised clinical trial. If there is any evidence that one option might be better than the other, then "not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial" (Angell 1997: 847). This rule applies to placebo-controlled trials as well. It is only ethical to compare a potential new treatment with a placebo when there is no known effective treatment. When effective treatment exists, a placebo may not be used and subjects in the control group must be given the best known treatment (Angell 1997: 847). Such a study is termed an equivalency study and the results are scientifically valid.

The 15 placebo-controlled trials were conducted even though it had been established that Zidovudine could significantly reduce the transmission of HIV from mother to child. According to Marcia Angell, the justifications for these trials are "reminiscent of those for the Tuskegee study: Women in the Third World would not receive anti-retroviral treatment anyway, so the investigators are simply observing what would happen to the subject's infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World."(Angell 1997: 847).

Several arguments have been advanced both for and against these trials but fall outside the scope of this paper and will not be pursued any further.
Both Tuskegee and the HIV Vertical Transmission Trials have been discussed to place in perspective the importance and relevance of ethical research in the Third World. I believe that it is as a direct result of the controversy ignited by the HIV Trials discussed above that much attention is being devoted to the proposed Vaccine Trials and research in general in the Third World.

International guidelines drafted as early as 1947 in the form of the Nuremberg Code and modified 20 years later in the form of the Helsinki Declaration, for the purpose of setting universal standards where human experimentation is concerned, have been shown to be problematic in the aforementioned Vertical Transmission Trials. It would appear as though research in the Third World is now becoming difficult.
While the Tuskegee experiment continued for 40 years before the ethical violations were exposed, the HIV Vertical Transmission Trials provoked an almost immediate and dramatic response from the medical profession itself. Hence, it is not surprising that even with the Vaccine Trials still years away in South Africa, ethical deliberation has already begun! Undoubtedly, the ethical component of clinical research in the developing world is gaining impetus.
It is with these ethical tensions in mind that I will examine the ethical issues pertinent to the proposed Vaccine Trials.

4.HIV Vaccine Trials in the Third World - the Four Principles Approach?

4.1 Introduction

The Nuremberg Code of 1947 requires that biomedical research be conducted in a manner consistent with four ethical principles: autonomy, beneficence, non-maleficence and justice (Loue 1996: 49). The applicability of these basic ethical principles within different cultural settings is increasingly being questioned. This is especially so because the international bodies who formulated these principles were unfamiliar with the different settings in which they would have to be applied (Barry 1988: 1083).

The Nuremberg Code, for that matter, was drafted in 1947 by the judges involved in the Nuremberg Doctors' Trial. The Declaration of Helsinki was written nearly 20 years later and was prompted by the limitations of the Nuremberg Code to provide specific guidelines to practitioners in the conduct of ethical research.

Hence, while the Declaration of Helsinki was the result of a medical professional body attempting to regulate itself, it was not without shortcomings. Many concepts are not clear, in particular, there is no guidance on how to resolve conflicts resulting from an attempt to maximise more than one principle simultaneously (Kunstadler 1980: 289-96). In spite of this, the Declaration of Helsinki has become the benchmark for ethical practice in research (London 1999: 812).

As such, it is important to establish whether this Western standard based on the Four Principles approach may be appropriately applied to biomedical research in developing countries.

4.2 Respect for Autonomy and Informed Consent

Translated from its Greek roots the word "autonomy" refers to self- rule. Western society emphasises autonomy – individual rights, self-determination and privacy- in its conception of personhood. The Nuremberg Code and its progeny require that participation in biomedical research be based on "freedom of individual choice, with no element of coercion or constraint. It dictates further that a person should understand the subject matter of the research sufficiently to make an enlightened decision"(Barry 1988: 1083). Hence all the details of the trial – the nature, duration and purpose of the trial, the methods that will be used, the possible effects on health and all the inconveniences entailed by the experiment - must be made known to the participant.
Such a conception of autonomy reflects the "basic premise of individual sovereignty"(Loue 1996: 49).

Applying this concept of autonomy and the requirements of informed consent can prove to be problematic in many cultures in the Third World where personal choice is extremely limited. In many African cultures the concept of personhood differs substantially from that in Western cultures. Personhood is defined by one's tribe, village or social group. In Western terms, selfhood emphasizes the individual. However, in certain African societies, selfhood cannot be extricated from a dynamic system of social relationships, both of kinship and of community as defined by the village (Barry 1988: 1083). This African concept of personhood is further elaborated by Augustine Shutte in his work on Ubuntu : persons exist only in relation to other persons. According to him, in all African languages, there is the local variant of the Nguni saying "umuntu ngumuntu ngabantu" – a person is a person through persons (unpublished data).
Similarly, in Ugandan culture, the wishes of the individual are often subordinated to those of the immediate or extended family. As such, participation of an individual in biomedical research may depend on the acquiescence or consent of another family member (Loue 1996: 49).
However, the concept of family consent is not peculiar to Africa alone. Family consent is an important concept in Japanese culture as well where it is seen as a reflection of the

role of family in Japanese society in general. As such, the principle of autonomy, as it exists in its traditional North American paradigm, is not entirely applicable to Japanese culture. Instead, Edmund Pellegrino refers to "something close to autonomy" that is respected in the context of Japanese society (Akabayashi 1999: 296-301).
Similarly, ancient Chinese medical ethics, established on the foundations of Confucian ethics, emphasises a respectful attitude towards one's patients based on an unconditional value for human life, but does not include respecting their autonomous choices (Tsai 1999: 315-321).

It is thus clear that where the notion of persons as individuals is not dominant, the consent process may shift from the individual to the family or community (Christakis 1988: 34).

Thus, an investigator seeking informed consent from individual persons in such settings may need to approach community elders for their consent before attempting to obtain informed consent from individual persons (Barry 1988: 1083).
The person acknowledged to be a "community leader" will vary from one culture to another. Whether this person meets the investigator's expectation regarding who can appropriately give proxy consent is another complicating factor.

In order to acknowledge the need for family consent in biomedical research in Uganda, a mandatory waiting period of 48 hours is allowed before an informed consent form is signed should the potential participant desire this option. This waiting period is, however, not without problems – transport to outlying areas may not be available, the entire process is costly and time consuming and, as a result, potential participants may abandon the trial altogether. Furthermore, the nature of the information regarding the trial may have been misunderstood in one sense or another, and in subsequent transmission to a family member or significant other, may undergo further modification. Under such circumstances, truly informed consent will not be obtained. However, with no suitable alternatives, this 48 hour waiting period remains an option when obtaining informed consent in Uganda.

An essential prerequisite related to proxy consent in Uganda is that a research participant must give his/her consent to participate; another individual could not consent for an unwilling individual (Loue 1996: 49). Nicholas Christakis echoes this sentiment in his appraisal of the ethical design of an AIDS vaccine trial in Africa.

Having established **who** will consent to participation in a research trial, it is essential to present the details of the trial to the prospective participant so that such consent is informed. This represents the "information element" of informed consent when material information is disclosed. Coupled to this disclosure is the element of understanding on the part of the patient (Beauchamp & Childress 1994: 145).
During a workshop held in South Africa to discuss ethical issues in HIV vaccine trials in September 1998, Oliver Ransome, the medical ombudsman, outlined the prerequisites for obtaining informed consent – a subject information sheet; third party adviser; time to reflect and the actual written consent. The details on the information sheet should include the overall purpose of the research " in comprehensible language". Confidentiality should be stressed and it should be clear that the subject is free to decline or withdraw. Questions should be invited and time should be allowed for reflection.

He highlights essential and crucial components of a subject information sheet, however, in South Africa, with very high rates of illiteracy, such a sheet may be inappropriate to use. In a similar workshop in Uganda, it was established that with their currently "high rate of illiteracy, many prospective research participants would be unable to read a form and understand it"(Loue 1996: 50). This would also have serious implications for obtaining the "written consent" referred to by Ransome.

Loue goes on to state that "Ugandans seem generally reluctant to affix their signatures to any document" especially one that "confirms their connection to foreigners". He also elaborates on the concept of "face agreement" in Uganda. Reluctance to signal one's agreement in writing may indicate "face agreement". This could be a reflection of cultural standards of etiquette or could reflect a "reluctance to make one's opinion known in negotiations characterised by an imbalance of power between the negotiating parties".

Most importantly, "face agreement" may result from an inability or unwillingness to comply with the terms of a written document and might increase the likelihood that research participants will later withdraw from the study (Loue 1996: 50).

Iliteracy coupled with language barriers in Africa, make the description of AIDS related studies difficult. When concepts like germ theory, viruses and vaccines are alien, it is indeed challenging to respond to Mark Heywood's (AIDS Law Project, University of the Witwatersrand) question on what is sufficient information for informed consent? Ron Bayer (HIV Centre, New York) also expresses concern regarding the explanation of "complicated scientific methods such as randomisation, placebos, vaccine inefficiency, the fact that participation in one trial may exclude future participation in trials of more effective vaccines and discrimination linked to participation".

An interesting problem with language was illustrated in the HIV Vertical Transmission Trials conducted on pregnant women in South Africa in 1997. In a report in the *Mail and Guardian*, October 1997, an attempt was made to justify the trials by explaining that informed consent was indeed obtained from trial participants. The placebo drug used in these trials was translated to the pregnant women as being a "spaza" drug or a "chuff-chuff"drug. While a "chuff-chuff" drug is understood to be a "pretend" drug, the word "spaza" is a colloquial term generally meaning "half the real thing" or a pretence of the real thing. It owes its derivation to the "spaza shops" which abound in most Black townships and which mimic real supermarkets. These "spaza shops", although expensive, are however, extremely functional and serve a vital purpose in townships generally located great distances from the formal shopping complexes and the central business districts. In no way are they associated with the concept of inertness inherent in a placebo. As such, the use of the term "spaza" to describe a placebo is clearly misleading. Participants might have been under the impression that they were receiving a weaker form of the active study drug instead of the fact of the matter which was simply that they were not receiving any drug at all.
Hence it is evident that the provision of information in a cross-cultural, Third World setting could prove to be a daunting task at the best of times!

An important point made by Heywood during the Vaccine Trial Workshop mentioned earlier is that informed consent should not be seen as static or stable but rather as a process which varies according to individual needs and circumstances. This belief was echoed by Graham Lindegger (Psychologist – University of Natal). He sees informed consent as a process which requires an in-depth understanding of how people make decisions. The process should begin with disclosure, followed by understanding in the absence of coercion and should culminate in consent.(Lindegger 1998; Vaccine Trial Workshop Document).

Beauchamp and Childress, in their description of informed consent, extend the process described by Lindegger by including two preconditions or threshold elements – competence (to understand and decide) and voluntariness (in deciding).

In the Third World, where research participants are usually poor, desperate and dependent, voluntariness is a significant precondition for obtaining truly informed consent. Such voluntariness implies independence from the manipulative and coercive influences of others. Research participants should be able to choose freely amongst alternatives and also have a right to refuse to participate.
Of the three forms of influence that may occur in a research setting, manipulation tends to occur rather than coercion or persuasion. In the context of decision-making in health care, informational manipulation tends to be the key form of manipulation employed. Misleading research participants, as in the case of using the word "spaza" to describe a placebo, is a form of deception that is clearly inconsistent with autonomous choice. Decisions are typically made in a context of competing influences, such as personal desires, familial constraints, legal obligations and institutional pressures. Where decision-making by patients and subjects is concerned, it is important to establish the point at which autonomous choice is impaired - although it is often difficult to draw a clear boundary between controlling and non-controlling influences. In research in developing communities, the prospective participants' subjective resistance to influence must be

assessed, not the objective resistance to influence or the reasonable person's ability to resist.

According to Beauchamp and Childress, the most difficult problem regarding manipulation in research is the effect of rewards, offers and encouragement. A flagrant illustration of an unjustified offer occurred during the aforementioned Tuskegee Syphilis experiment. Subjects were offered free burial assistance and insurance, free transportation to and from the examinations and a free stop in town on the return trip. They were rewarded with free medicines and free hot meals on the day of the examination. The socioeconomic deprivation of these subjects made them vulnerable to these overt and unjustifiable forms of manipulation (1994: 166-167).

While it is easy to differentiate between various forms of influence theoretically, many borderline cases exist in practice, especially in research settings. An offer that is made in a setting in which it is abnormally attractive is clearly manipulative, but not coercive as there is no threat involved. Attractive offers such as free medication or extra money can leave persons without any meaningful choice apart from accepting the offer largely because such persons are constrained in a desperate situation. Whatever we may decide to call this, it is widely held that offers of this magnitude to a person in desperate need is inherently exploitative and is not consistent with autonomous choice.

In Uganda, it was decided that the low income of many people as well as the disempowered status of women could preclude a truly free decision to participate in a research trial. As a result, incentives, in the context of participant recruitment and retention, was deemed problematic due to the resultant absence of a perceived choice in decision-making. Incentives which were approved of included reimbursment for wages lost as a direct result of study participation, such as attendance at study clinics or interviews; reimbursement for transportation costs to the study site and meals at the study site when the individual was required to be at the study site during a regular meal time. Other forms of incentives were found to be "so extraordinary as to be coercive" (perhaps manipulative would be a more appropriate term), including cash payments, bicycles and

medical care for illnesses not associated with the disease or treatment under study (Loue 1996 ; 50)

Looking specifically at the ethical design of an AIDS vaccine trial in Africa, Christakis warns researchers that "it is difficult to avoid coercing subjects in most settings where clinical investigation in the developing world is conducted. African subjects with relatively little understanding of medical aspects of research participation, indisposed toward resisting the suggestions of Western doctors, perhaps operating under the mistaken notion that they are being treated, and possibly receiving some ancillary benefits from participation in the research, are very susceptible to coercion. Their vulnerability warrants greater care in procuring consent and necessitates greater sensitivity to protect this class of research subjects."(1988: 35)

Closer to home, a study conducted in Durban to assess whether informed consent for HIV testing in a South African hospital was truly informed and truly voluntary, yielded interesting results. Of the 56 women studied, 88% felt compelled to participate, even though they were assured that their participation was entirely voluntary. Twenty-eight percent of the women "perceived the research to be integral with the service at the hospital and agreed to the HIV test because they thought that refusal would compromise their care. This subtle coercive element may stem from the social context of a hospital where the health professionals are held in high regard".

This study illustrates a phenomenon characteristic of health care systems in the Third World - namely - limited resources. When patients have little recourse to alternative medical care, they may have no choice but to participate in a research study conducted at the only tertiary hospital at their disposal. It is highly probable that informed consent sought under such circumstances might be "less than voluntary".

This study concludes that "subtle and unexpected elements of coercion can reside in the perceptions (real or imagined) held by patients recruited into a research project in a medical care setting" (Abdool Karrim 1998: 640).

A discussion on informed consent would be incomplete without examining the important precondition of competence. In biomedical contexts a person has been viewed as competent if able to understand a therapy or research procedure, to deliberate regarding major risks and benefits, and to make a decision in light of this deliberation (Beauchamp & Childress 1994: 136). The legal standards for competence include the four related skills of "communicating a choice, understanding relevant information, appreciating the current situation and its consequences and manipulating information rationally"(Appelbaum 1988: 1635).

The label of "incompetence" has traditionally been applied to children, the mentally retarded, people with major psychiatric illnesses and those with delirium or dementia. This group of people is regarded as vulnerable research subjects because they lack capacity to give informed consent and because they depend on others to protect them (Kopelman 1994: 2291).
Little attention has been paid to the millions of people in developing countries who due to poverty, malnutrition and lack of opportunities for education are either illiterate or uneducated. Coupled to this are the constraints of cultural belief systems especially where causation in illness is concerned. To these people, many concepts in science and medicine are alien and they often have to undergo an enormous paradigm shift in order to understand and deliberate about the complexities of Western biomedical research.
This group of people also falls into the category of "vulnerable research subjects" because fear, ignorance or pressure may account for their agreement to participate. Too little protection of these subjects risks their exploitation; too much protection risks unjustified paternalism (Kopelman 1994: 2292).

At the risk of the latter charge, I believe that it is highly probable that in many cases of biomedical research in the developing world, subjects, although adult and not mentally impaired or retarded, do not fulfil all the criteria for competence outlined above.
Often, subjects do not understand what they have been told about a complicated and foreign research protocol and when they do not understand they are not competent to decide whether to accept or reject their involvement in such a setting. The capacities

necesssary for such understanding include "a memory for words, phrases, ideas and sequences of information". Furthermore, the "chance nature of the occurrence of risks and benefits highlights the importance of the ability to understand causal relations and the likelihood of various outcomes. Finally, it may be important for patients to be able to understand not only what they are told, but also that they have a critical part to play in the decision-making process. Deficits in attention span, intelligence and memory may detract from these abilities"(Appelbaum 1988: 1636).

It is not my intention to suggest that all people from developing communities are incompetent and hence cannot give informed consent to participate in research conducted in the Third World. This would deprive such subjects of their decision-making rights and would represent a serious infringement of liberty. Rather, it is possible that a position of "limited competence" exists in many instances.

The point I wish to make, based on more than 10 years of experience in the medical field in South Africa, is that patients have great difficulty in understanding basic concepts in health and disease, even where language barriers do not exist, and hence rely heavily on the "doctor's best judgement" when choices have to be made. Hence, there is a large patient population who clearly do not meet all the criteria for competence.

Then, there are others still who do not think they are in a position to make their own decisions. Unfortunately, in the aftermath of the apartheid era in South Africa, many people who are completely competent still relinquish their decision-making rights to authority figures, be they doctors or researchers or both. Many people still devalue their capacity to understand and deliberate and make choices and the phrase "Doctor, you know best" is a frequent resignation of far too many patients.

As these are adult patients without mental illness or retardation, but rather with problems or understanding related to educational levels and language and cultural barriers, enormous efforts are indicated on the part of the medical profession and researchers to meet the level of understanding necessary to meet the criteria of competence.

Coupled with this is a need for empowerment of patients so that they can exercise their decision-making rights.

It is evident from this discussion on the procurement of informed consent from prospective participants in HIV vaccine trials that the concept is riddled with intricacies. The precise demands of the principle of autonomy are largely unsettled and remain "open to interpretation and specification".

That the process of informed consent requires **time** in ideal circumstances, and more so in underdeveloped communities, is undeniable. Massive education campaigns, as well as the recruiting and training of translators from within target communities with their involvement throughout the study period will be vital to the ethical performance of such trials in South Africa. Only then can understanding of research procedures be ensured, only then will true informed consent be obtained.

There is no doubt that where informed consent is concerned, we need to avoid the pressure to act unethically because of the urgency of the situation (Heywood 1998: 6).

4.3 Non-maleficence and Beneficence

While non-maleficence is associated with the maxim of *primum non nocere* - "first, do no harm", beneficence encompasses both an obligation to do good and an obligation to protect research participants from harm.

Researchers need to make efforts to secure the well-being of research participants. This entails achieving a favourable balance between the risks and benefits of the proposed research (Loue 1996: 50).

What risks will be faced by participants in an HIV Vaccine Trial?

To begin with, adverse effects of the vaccine itself may occur as with other vaccines in current use, such as pain or infection at the injection site, fever or allergic reactions. Although studies undertaken in the United States have indicated that the vaccines used have "relatively few short-term side effects of minor functional consequence, the public perception is one of wariness with regard to their safety" (Jenkins 1995: 36).
A study conducted in Thailand among high-risk populations to assess willingness to participate in AIDS vaccine trials found that 25% of the 2180 subjects interviewed would definitely join a trial if asked. An additional 38% would accept an AIDS vaccine if they were convinced it would be safe and effective. Vaccine side effects were considered to be important barriers to trial participation with up to 60% of the study sample being concerned about short-term side effects and up to 55% being worried about long-term side effects- like permanent injury or death (Celentano 1995: 1079).

More specifically, with an HIV vaccine, participants are likely to be concerned about actually developing HIV disease from the vaccine. With the current use of genetically altered or killed viruses, this risk is unlikely. The current subunit vaccine candidates, which employ genetically engineered proteins from the HIV envelope - with a piece of

the virus being used - are likely to allay much anxiety. However, participants' fears are likely to magnify as vaccine developers incorporate the use of whole killed or live attenuated virus. Already, scientists are becoming impatient to test live attenuated virus vaccines! However, leading clinicians are still hesitant regarding the safety of such vaccines. While some scientists have demonstrated immune protection lasting for more than 7 years in monkeys vaccinated with live attenuated SIV, the monkey analogue of HIV, at least two unpublished studies on monkeys raise concerns about a fraction of animals who actually develop disease in time (Wadman 1997: 426}. In support of this, Ruth Ruprecht, of Boston has data on 18 monkeys exposed as adults to live-attenuated virus. After a follow up period of 18 months, "one animal has developed early-stage immune problems and another has full-blown AIDS". Hence, it is not surprising that the majority opinion at present is that "there is just not enough evidence that a live-attenuated HIV-1 vaccine is safe-or effective"(McCarthy 1997: 1082).

Even with current genetically engineered vaccines, while it is possible that disease will be prevented, infection might still occur. In fact, vaccines rarely prevent infection, instead, they prevent or modify disease. In general, vaccines tend to "reduce the number of invading micro-organisms, increase the rate of clearance of the infection, prevent the secondary consequences of infection or prevent transmission. Similarly, few of the candidate HIV vaccines appear promising for preventing infection, and the expectation that HIV vaccines will in fact prevent infection is yielding, in the scientific community, to the hope that they may prevent disease" (Bloom 1998: 186).
In reality, when the first AIDS vaccine trials were launched in the United States and Thailand in 1998, using the HIV envelope protein, gp120 in a vaccine called AIDSVAX, two outcome measures were to be assessed – "infection by HIV and viral load in those infected".

Furthermore, the possibility of vaccine failure is a very real one and the occurrence of "breakthrough HIV infections" or disease cannot be excluded.

This particular risk to the subject needs to be assessed in the context of the different types of trials that are performed.
Safety (phase 1) trials and immunogenicity (phase 2) trials usually are conducted in developed countries using small numbers of people at low risk of HIV infection. Efficacy (phase 3) trials, on the other hand, require large numbers of participants at high risk to develop HIV infection. It is reasonable to assume that the risk of developing HIV infection during the course of phase 1 or 2 trials by low risk participants will be far greater than the risk taken by people entering phase 3 trials, already at high risk by virtue of lifestyle or other predisposing factors.

This brings us to the crucial question regarding HIV vaccine trials in the Third World - will researchers have an obligation to provide anti-retroviral treatment to subjects who become infected during the course of the trials ?

Scientists and ethicists are clearly divided on this point.
Scientists and researchers are concerned that treatment with anti-retroviral drugs will compromise the ability of the trial to measure the efficacy of the vaccine in preventing disease (Bloom 1998: 186).

A critical measure of the success of an AIDS vaccine trial would be whether the vaccine lowers the "viral load" - the amount of HIV in the blood - in people who get infected. Anti-retroviral treatment will also lower the viral load. If many of the participants who become infected begin taking potent anti-retroviral drugs, reduction in viral loads due to the vaccine cannot be assessed. Scientists fear that it will become impossible to design a "scientifically valid" trial if there is widespread use of anti-retroviral drugs.
However, the head of the biotech company VaxGen, that launched the first efficacy trials of an AIDS vaccine in the United States, argued that not everyone would start treatment immediately, and because researchers would be taking blood from participants every 24 weeks or so, they should be able to make at least one viral load measurement in many untreated people who become infected (Cohen 1998: 22).

Delaying drug treatment until viral loads can be measured, as is implicit in the trial design by VaxGen, however, only adds to the complex ethical problems already inherent in treating participants who develop HIV infection during the trials.
This delay in treatment will pose problems in the developed world, in particular, because in developed countries, it will be ethically required that individuals in vaccine trials who have acquired HIV infection will be offered anti-retroviral therapy. It is also expected that a delay in treatment will not be tolerated in the West.

Can these problems be circumvented by conducting trials in the developing world, where resources are not available to provide anti-retroviral drugs ?
The standard of care in the developing world is clearly "no treatment for HIV/AIDS".
This will also obviate the ethical dilemma of delaying treatment to measure viral load.
A perfect solution, it would seem!

However, ethical guidelines on human experimentation in international research, do not condone this. The two documents most influential in this regard are the Declaration of Helsinki, promulgated by the World Medical Association in 1964 and the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" published by the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), in 1982.
The most recent version of the CIOMS guidelines, prepared in 1993, is explicitly intended to indicate how the ethical principles of the declaration can be applied effectively in developing countries.
These documents are accepted by the international medical community as providing for the highest standards of medical ethics in human experimentation.
CIOMS Guideline 14 quotes article II.3 of the Helsinki Declaration and states that, "In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method"(Bloom 1998: 186-187).
In HIV/AIDS, this constitutes anti-retroviral triple therapy.

Various attempts have been made to circumvent the application of these ethical guidelines where HIV/AIDS is concerned. However, in many cases such arguments revolve around semantics of what the "best proven diagnostic and therapeutic method" constitutes. Other arguments against treating trial participants who develop infection regard the treatment as an undue influence to encourage trial participation.

Ultimately, the crucial issue is one of economics. Multinational drug companies are not prepared to invest the large sums of money necessary to perform research in keeping with the existing ethical guidelines.

This question of treating trial participants with anti-retroviral drugs if they develop infection during the trials remains largely unanswered. During a workshop in South Africa in 1998, the issue was skirted, stating that this issue would be left up to the host country to decide.
An idea of what is likely to happen in South Africa may be extrapolated from what is already happening in Thailand. In a large trial funded by VaxGen, neither the company nor the cash-strapped Thai government plans to give cutting-edge treatments to people who become infected.
It is obvious that setting a lower standard for poor countries would create a slippery slope - when the level of ethics is set below the maximum, it's very easy to lower it more (Cohen 1998: 23).

More complicated than the actual physical and medical side-effects of vaccination, are the so called "social harms" that may burden participants in a vaccine trial.
These may result from simple participation in trials or from testing HIV positive as a result of vaccination. Individuals whose participation in vaccine trials becomes known may be identified as high risk for AIDS, or may be mistakenly assumed to have AIDS. In a study conducted in Thailand in 1995 amongst high-risk populations to assess willingness to participate, 24-49% believed that their partners would refuse to have sex with them after immunization (Celentano 1995: 1079).

Discrimination based on HIV antibody status may occur in a number of settings - acceptance into the military, the job corps, the peace corps or the foreign service; the purchase of life, health or disability insurance; permission to immigrate or travel abroad or incarceration (occasionally even arrest, particularly for sex crimes). It is clear that volunteers who develop antibodies as a result of vaccination may be at added risk for discrimination (Hodel 1994: 256). While it is possible to distinguish between HIV positive results from a vaccine as opposed to natural infection using different laboratory tests, many potential participants might be unaware of this, hence this will be perceived as a significant risk.

The possibility of being included in a control group in the trial, where a placebo will be used instead of the HIV vaccine will also shift the risk-benefit ratio in a rather negative direction. Researchers in Philadelphia have already reported that interest in participating in a vaccine trial amongst intravenous drug users dropped from 47% to 24% when the possibility of using a placebo was mentioned (Jenkins 1995: 37).

Finally, a further risk inherent in an HIV vaccine trial is the possibility of increased risk-taking behavior by participants who mistakenly believe that they have been protected by the vaccine.

What are the benefits, if any, to trial participation ?

As scientists weigh the potential benefits of conducting a trial against the potential risks, so too will individual participants and target communities weigh relevant data before deciding to participate. This risk-benefit calculus will ultimately be informed by social values. This is of special relevance to the Third World where in communities already "burdened by violence, drugs, alcohol, unemployment, urban decay and the like, the AIDS epidemic has merely exacerbated an already arduous burden of day-to-day survival. For many inner city residents the threat of random gunfire easily exceeds the somewhat less immediate threat of HIV infection, a risk profile that is difficult for outsiders to appreciate" (Hodel 1994: 255).

This sentiment is echoed by Virginia van der Vliet in her book "*The Politics of AIDS*", in a chapter entitled " The Savagery of Life: Powerlessness and Vulnerability":-
"Increasingly, those affected are the poor in urban ghettos, illegal migrants, drug users, street children, prostitutes, or the impoverished people in Third World countries. They are not unacquainted with the savagery of life. For them, AIDS is just an additional problem, often faced with their customary fatalism. Fatalism is no protection against AIDS." (van der Vliet 1996: 77-78).

It is against this backdrop of fatalism that one needs to assess whether the development of a protective vaccine against AIDS will be perceived to be of overwhelming benefit to the Third World.

Thus far the benefits cited have been located at two extremes of a narrow range of limited possibilities. Subjects may be motivated to join a trial either on altruistic grounds or on grounds of personal benefit.

A few studies have been conducted to date to assess the motivation of people to participate in trials. In one such study in Thailand, it was found that personal benefits were particularly important to the most willing group. This included additional direct benefits to study participation, primarily with respect to health care like long- term follow- up, provision of long-term care for non-vaccine related medical concerns. Purely altruistic motives were unrelated to willingness to participate (Jenkins 1995: 40-41).

Similarly, another survey of 2180 Thai people, found that the principal inducement to join a trial was health insurance (62% of subjects). These respondents indicated that a 5-year family health insurance plan would encourage them to join a trial (Celentano 1995: 1079- 1082).

Where HIV vaccine trials are concerned, the risk- benefit ratio is situated in a rather precarious position. It is clear to see that participants have little to benefit personally from such trials and potentially much to lose!

It is therefore not surprising that low levels of participation have been reported in trials so far.

In a French vaccine trial, only 57 of 645 persons who had expressed initial interest by mail actually enrolled in the trial. Other surveys have found that under the relatively hypothetical condition of being asked to join a phase 2 or 3 HIV vaccine trial, levels of willingness have ranged from 37% to 84%.

Studies that have gone beyond asking the simple question of whether participants would be willing to join a trial have found that interest dropped dramatically when specific trial features or procedures were explained.
A study of intravenous drug users in the New York City area found that the percentage of "very interested" potential volunteers dropped from 50% to 17% after they received information normally contained in a consent form.
Another study found that 73% of those approached in Baltimore were interested in participation, although this figure dropped to 49% after the issue of testing HIV antibody-positive as a consequence of immunologic response to the vaccine was discussed (Jenkins 1995: 37). Both studies were conducted on people at high risk to develop HIV infection!

Interestingly, studies are also finding that willingnes to participate in these trials is associated with lower levels of education. In a Thailand study of 255 participants, high school-educated respondents were more willing to participate than university graduates (Jenkins 1995: 39). One wonders whether this choice not to participate by more educated respondents is not the result of a more accurate appreciation of the risk-benefit ratio inherent in these trials, namely the high risk- low benefit scenario.

Of significance, in these studies of willingness to participate in trials, is the finding that the highest level of interest has been expressed in developing countries where the epidemic has universally impacted on kinship networks and community life - in Haiti and Kenya. This concept will be discussed in greater detail later.

A paper from Uganda highlights some of the issues that have been raised already. The potential difficulties associated with participation in research included the possibility of stigmatization as an individual with a particular disease, difficulties in obtaining transportation, the potential for a breach of confidentiality and ostracism by the patient's family or community. The primary benefit was that of potential access to medical treatment for the particular condition under study. It was concluded that patients would almost invariably agree to participate for this benefit alone, regardless of the potential risks associated with the research (Loue 1996: 51).

An interesting point that has emerged from this discussion is that given full details of the risks and benefits of an HIV vaccine trial, participants will either exercise their right of refusal to participate or will agree to participate only if the benefit is maximised in terms of personal incentives, in particular health care, in the developing world.
This raises the question of the extent to which the principles of beneficence and non-maleficence should be maximised relative to the principle of autonomy but this will be explored later.

A crucial factor to be considered here is that in order for the benefits to outweigh the risks in the trial of an HIV vaccine, an individual would have to be at some risk of HIV infection. The necessity of being at risk therefore has scientific and ethical import.

4.4 Justice

The principle of justice or fairness requires that the benefits and the burdens of research be equitably distributed among individuals or communities. No single group can be required to bear a disproportionate share of the risk or be favoured with a disproportionate share of the benefits (Loue 1996: 51)

Under the principle of justice, research subjects should be chosen "for reasons directly related to the problem being studied," and not "because of their easy availability, their compromised position, or their manipulability." As a result, the "practical concerns that make an AIDS vaccine trial easier to conduct in Africa do not alone constitute sufficient justification to use Africans as subjects. Only the scientific concerns related directly to the problem of establishing the ability of a vaccine to prevent HIV infection are relevant"(Christakis 1988: 36).

Where HIV/AIDS is concerned, it is evident that this disease is rampant in Africa. As a result, it may be unavoidable that a higher degree of research risk is tolerated in order to deal with the problem and this may even be socially sanctioned. However, this does not mean that Westerners should "indiscriminately benefit from research conducted in Africa if Africans are systematically subjected to excess research risks with the prospect of deriving but little benefit. This would violate the principle of justice"(Christakis 1988: 36).

Where an AIDS vaccine is concerned, much of the world stands to gain from the development of an effective vaccine. In keeping with the principle of justice, those who stand to benefit from the vaccine should also bear the burden. Hence, the research risks should be fairly distributed as should the benefits. Vaccine development trials need not be restricted to the African continent.

In Africa, undoubtedly, much of the population stands to gain from the introduction of an effective vaccine. However, economic constraints may prevent adequate distribution of

such a vaccine. The benefits to Africans are thus "only hypothetical unless there is a financial commitment by the developed world to provide the vaccine. In this light, it would be frankly unethical to subject Africans to a disproportionate share of the research risks" (Christakis 1988: 36)

CIOMS Guideline 15 on Externally Sponsored Research requires that any trial "must be responsive to the health needs of the host country... Any product developed through such research (should) be made reasonably available to the inhabitants of the host community or country at completion of successful testing" (Bloom 1998: 186-187).

A contingency of any trial of an AIDS vaccine in Africa by Western scientists should thus be to provide access to the technology once it is developed - possibly in the form of free or subsidized vaccine (Christakis 1988: 36).

In South Africa, the HIV Vertical Transmission trials are an excellent example of the violation of the principle of justice in a research setting. In 1999, two years after the completion of these trials to find shorter courses of anti-retroviral treatment for HIV infected pregnant women, millions of eligible women still go without treatment. It has clearly been shown that these shorter regimes of treatment are effective. Yet, there appears to be no funding forthcoming from the South African government or from the developed world, in particular, the United States, who were involved in these research trials.

In a paper published in the *American Journal of Public Health*, this issue is discussed openly. The outcome of the trials performed on impoverished populations around the world was clearly not the delivery of the necessary drugs to these developing countries. Instead, the purpose was "to provide information that the host country can use to make a sound judgement about the appropriateness and financial feasibility of providing the intervention"(Annas 1998: 561). This is ethically unacceptable. Good intent in the absence of a sound plan to provide the intervention, once proven to be effective, is no justification for the performance of such research

Annas goes on to say that "Unless the intervention being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gained from the clinical trials for the developed countries' own benefit. If the research reveals regimens of equal efficacy at less cost, these regimens will surely be implemented in the developed world. If the research reveals the regimens to be less efficacious, these results will be added to the scientific literature, and the developed world will not conduct these studies"(1998: 561).

Hence, it is imperative that "African countries involved in the clinical trials must make realistic assurances that if a research regimen proves effective in reducing mother-to-fetus transmission of HIV, resources will be made available so that the HIV-positive pregnant women in their countries will receive this regimen"(Annas 1998: 561).

Once again, with the proposed vaccine trials, South Africa has not clarified that it will conduct these trials on condition that a definite plan is in place to acquire the vaccine for widespread use, if it proves to be effective.

Of note, however, is the fact that South Africa has decided not to conduct trials using a clade B vaccine which has already been developed in the United States. This viral subtype is not common in Sub-Saharan Africa but it is the predominant clade in North America where homosexual transmission of HIV is common. In South Africa, with a predominantly heterosexual transmission of disease, the predominant subtype is clade C. South African researchers have opted to rather develop an appropriate clade C vaccine for experimentation here. Conducting trials of a vaccine that would have largely benefited the developed world would have been a clear violation of the principle of justice.

Yet another way in which the principle of justice can be violated involves the counselling of trial participants to continue practising other preventative measures - like safe sex,

condom use, single partners - after the vaccine has been administered. With the promotion of these measures, it will be difficult to assess vaccine efficacy. These interventions could diminish the ability of the study to detect a difference between true vaccine recipients and controls by decreasing the incidence of HIV infection in all participants for reasons unrelated to vaccine status (Christakis1988: 34). On the other hand, failing to stress these measures could result in a greater risk of contracting HIV infection, especially if the vaccine proves to be ineffective.

To circumvent this problem, a larger study group would be required to detect the relatively smaller measured influence of the vaccine. As a result, more individuals will be exposed to the experimental vaccine and the cost of the trials will be higher. It will also take longer to get statistically significant results.
To prevent this potential harm to participants and in all fairness to them, it is imperative that researchers continue to promote preventative measures other than the vaccine.

Finally, in Uganda, it was discovered that fairness to trial participants could potentially be affected when members of Institutional Review Boards or Ethics Committees and participants belong to different tribes. As a result, members of one tribe could potentially be over-researched and hence bear an unfair share of research risk. To overcome this problem, one needs to be cautious in how one constitutes review board or ethics committees (Loue 1996: 51).

Hence, it is evident that there are many loopholes in performing ethical biomedical research, especially in the Third World. Under no circumstances should the principle of justice be violated in the design of an HIV vaccine trial.

4.5 Relevance of the Four Principles in Africa

It is obvious from the preceding discussion that the principles are "far from comprehensive and lack extensive guidance on issues of major importance, including the simultaneous maximisation of principles or the prioritizing of conflicting principles. Moreover, they are Western constructs and, as such, do not take into account local customs and traditions that should be respected and incorporated into the research process to the extent possible" (Loue 1996: 51).

Respect for Autonomy:

Respect for autonomy, in the African context differs significantly from the Western definition. This is so because the concept of personhood differs substantially. Where the embeddedness of the individual within society is emphasised, individual informed consent may be difficult to solicit. In such settings, proxy consent becomes important but should not take precedence over the wishes of the individual. Rather, the consent may have to be obtained jointly or after time has been allowed for consultation with significant others. In a Third World setting, this may entail travelling to rural homes and allowances will have to be made in this regard.

The information element of informed consent will also differ significantly in Africa. Written information as well as written consent may be inappropriate in the context of high rates of illiteracy. As a result, information will have to be available in oral or visual forms. Language barriers are unavoidable and hence all information regarding the trial will have to be available in the language/s of the trial participants. Interpreters, from within the target communities, will be indispensable. It will also be essential that all scientific and research protocols are explained in culturally relevant terms.

In a Third World setting the pre-condition of voluntariness in soliciting informed consent is crucial. This is so because socio-economic deprivation renders participants vulnerable to the most subtle forms of influence. It is thus essential that participants are reimbursed

for losses sustained directly related to trial participation. Anything in excess of this will be seen as extraordinary and will constitute an unfair inducement.
The concepts of voluntariness and informed refusal are also affected if resources are limited and if research is conducted at academic hospitals. Patients often have no alternatives for treatment and feel compelled both to consent and participate. These relatively few centres of excellence in the field of health care are held in high regard as are the medical staff of these institutions. As a result, patients will comply with requests for participation in research as an indication of respect and gratitude for health services. In such settings, informed consent is less than voluntary.

Finally, under the principle of autonomy, competence to give informed consent in the Third World is becoming a volatile issue. More and more, it is being realized that in "most settings in Africa, informed consent will be problematic and difficult, and it may even preclude ethical research. This is because, in the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as "better than nothing" and research will almost inevitably be confused with treatment, making informed consent difficult" (Annas 1998: 562).
Support for this conclusion was elicited in interviews with trial participants in the Ivory Coast where it was found that "many of the participants did not understand the implications of the trial, even though they gave their consent". In the words of an African researcher, "in an environment where the majority can neither read nor write and is wallowing in poverty and sickness, hunger and homelessness, and where the educated, the powerful, the rich, or the expatriate is a semi-god, how can you talk of informed consent?" (Zion 1998: 1330).

While such a viewpoint is regarded as paternalistic, it may nevertheless reflect the reality of research in Africa. This, however, should not preclude ethical research in Africa, but should be remedied in the form of widespread education campaigns so that, in time, it will be possible to elicit informed consent from truly competent research participants.

Non-maleficence and Beneficence:

In the context of Third World settings in Africa, balancing these two principles in the form of the risk-benefit ratio has already been shown to be problematic. The odds are leaning heavily in the direction of high risk-low benefit especially if the intervention being tested is not made available to the Third World after the trials. The risks to the individual are many and serious. Apart from the usual physical or medical adverse effects, social harms are significant in Africa, where much stigmatisation is attached to having HIV/AIDS.

The benefits, while appearing to be significant in terms of the HIV/AIDS pandemic, are minimalised by the ethos of fatalism in those communities who bear the brunt of this devastating illness. Under these circumstances, it appears as though only those at high risk of developing HIV/AIDS will derive benefit. The risk-benefit ratio can also be viewed in terms of the Belmont Report which requires that "risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society..."(Christakis 1988: 35).

Any principles which prevent harm to research subjects and demand their beneficient treatment are particularly relevant in a Third World setting where vulnerable subjects need more protection than usual. Without such stringent ethical guidelines, these subjects run the greatest risk of exploitation by rich and powerful developed nations.

Justice:

The fair distribution of the benefits and burdens of HIV vaccine research in Africa is an absolute requirement of ethical research. The higher incidence of HIV/AIDS in Africa does justify a higher tolerance of risk but not to the detriment of the African people. If the only people who will benefit from vaccine research are the developed nations of the world, this research cannot be justified in Africa. It is therefore imperative that a definite plan is in place to ensure that a vaccine, if found to be effective, will be made available to the people who need it most and who have borne the brunt of a very risky research trial.

Undoubtedly, the basic ethical principles that guide human investigation, as defined by the Helsinki Declaration and the Nuremberg Code, need to be interpreted and applied within different cultural settings.

In Africa, "making respect for autonomy a trump moral principle, rather than one moral principle in a system of principles, gives it an excessive value...In many clinical circustances the weight of respect for autonomy is minimal, and the weight of nonmaleficence or beneficence is maximal. Similarly, in public policy, the demands of justice can easily outweigh the demands of respect for autonomy"(Beauchamp and Childress 1994: 181).

In the Third World, it appears as though the principles of beneficence, non-maleficence and justice should be maximised relative to the principle of autonomy. It is obvious that by using material inducements to shift the risk-benefit ratio in a positive direction, voluntariness of informed consent is compromised. However, fair distribution of the benefits of the research, in the form of an effective vaccine, would justify some of the research risk taken by impoverished Third World populations. At the same time, sincere efforts to obtain truly informed consent should not be abandoned.

5. Research and its limitations on the moral interests of subjects

The discussion thus far has illustrated that medical research involving human subjects creates conflicting values. On the one hand, we seek to enhance the general welfare of society by expanding our generalizable medical knowledge - the development of an effective HIV vaccine will meet this objective. On the other hand, the traditional nature of research studies may unavoidably involve some compromise of the moral interests - the rights and welfare - of human subjects.

These moral interests fall into three categories:

1. the interest in exercising the capacity for moral choice
2. the interest in avoiding harm
3. the interest in fair treatment

Acceptable limitations on these moral interests need to be established. This may be achieved with the following moral framework proposed by Ackerman and Strong:

1. The Social Benefit View

Here, limitations on moral interests may be tolerated if they promote the interests of research. The benefit of generalizable medical knowledge takes precedence over the rights of the individual. Carried to its logical conclusion, it would permit unacceptable violations of the rights and welfare of individuals as occurred in the Tuskegee experiment. This is by far an inadequate approach and will not be examined further.

2. The Subject-Oriented Approach

The moral interests of the subject are given priority over the interests of research. This approach emphasizes informed consent, limitation of risk and fair treatment of subjects. Research will be permitted only if these requirements are satisfied.

3. The Balancing Approach

Using this strategy, the social benefits of medical research and the moral interests of subjects are integrated. This approach forms the basis of the Belmont Report in which the risk to the subject must be outweighed by both the benefit to the subject and the benefit to society. The risk-benefit profile affecting the immediate subject is usually given special weight. It is clear that in assessing this balancing process, the degree of risk at which subjects will be placed, will be pivotal.

Problems related to Consent:

As discussed previously, the elements of information, comprehension and voluntariness are critical in obtaining informed consent. Each of these elements may be explored looking at the subject-oriented view as opposed to the balancing approach.

Information

The moral interests of a subject might be at issue if limited or inadequate information were provided. In the context of the HIV vaccine trials, if participants were NOT told that they would NOT be able to participate in future vaccine trials, this would constitute limited or inadequate information.

A subject-oriented view requires strict observance of the information condition. Deceptive nondisclosure of pertinent information would be prohibited because subjects are deprived of "their right to decide freely and rationally how to invest their time and persons". It would thus be impermissible to ask subjects to consent to the nondisclosure described above.

By contrast, a balancing approach would permit nondisclosure of information if it is necessary to achieve research objectives and subjects will not be placed at significant risk. Here, while there is some risk involved in participating in trials of less developed vaccines, being denied the opportunity of participating at a later stage, with a more

advanced and hence more effective vaccine, relatively speaking, might not constitute a significant risk to the individual. In this hypothetical case, if this information were disclosed, initial trials might never start, if all potential participants waited for a better vaccine.

On the other hand, if trial participants were NOT told that they would NOT receive treatment if they developed HIV/AIDS during the course of the trials, this nondisclosure would place the subjects at considerable risk and could not be justified using either the subject-oriented view or the balancing approach.

Comprehension

If, in the course of obtaining informed consent, it was discovered that a potential participant, due to educational and cultural factors, could not understand the details of the scientific process involved in research in terms of randomisation, blinding, placebo-control - even though it was explained in simple terms - but was prepared to give consent nevertheless, how could this be justified?

For a subject-oriented approach, valid consent must include adequate comprehension of the consequences of involvement. This participant may not be able to appreciate the consequences of receiving placebo. The consent obtained would not be valid and, s/he should not participate in the trial. In Africa, this would exclude a significant number of potential participants, perhaps to the extent that vaccine research may not be scientifically valid due to small numbers participating in the trials.

A balancing strategy may permit less than fully adequate comprehension when the latter is unavoidable and participation in research will not seriously compromise the subject's welfare. However, even this approach could not justify proceeding with the consent, because the risk to the participant in an HIV vaccine trial is great and comprehension of this risk cannot be compromised. Without the vaccine, of course, the participant and society at large, is also at risk and perhaps the lesser of two evils need to be considered. In the absence of educational upliftment in Africa, this might become a necessary option.

Voluntariness

A study conducted in Thailand and referred to earlier explores the issue of providing incentives like a 5- year health insurance plan to potential trial participants in an HIV vaccine trial. 62% of participants agreed to participate if they could receive this incentive. Is this justifiable?

A subject-oriented approach requires that the subject's decision to participate represent an adequately voluntary choice. To ensure that the decision reflects the subject's values and interests, one would have to appeal exclusively to the subject's willingness to accept risks or inconveniences for the benefit of society. This means that payment offered should be restricted to fair compensation for the time expended and the inconveniences endured by the subject. Payment should not be so high as to provide an independent motive for participation.

A balancing strategy may not regard the use of an incentive as an unacceptable compromise on the voluntariness of choice. Payments for research participation may be set at levels necessary to secure the required number of subjects, provided that subjects will not be placed at significant risk.

Problems Related to the Risk of Harm

The following protective conditions safeguard the welfare of research subjects:

1. not exposing subjects to the risk of harm without their consent
2. preventing harms that may be unnecessary or inappropriate - this requires that human subjects should not be used when research objectives can be achieved without their involvement; that the least risky procedures are used and that the risks are reasonable in relation to anticipated benefits
3. ensuring that doctors relieve the harms caused by disease when providing treatment in the research setting.

In isolating incremental harm, one may distinguish between therapeutic and non-therapeutic research procedures:
Therapeutic research procedures are intended to benefit subjects, as well as to contribute to the achievement of research objectives - the HIV vaccine is an example. If this treatment modality is not as effective or safe as an alternative treatment, then it may carry a risk of incremental harm.
Non-therapeutic research procedures are only intended to contribute to the achievement of research objectives; they are not intended to benefit subjects - such as medical procedures like venepuncture or bone marrow aspirations. Hence any associated risks are incremental.

Moral problems related to the welfare of research subjects arise when the subject's limited capacity to consent or the design of the research project requires modifications to the protective conditions described above.
A subject-oriented view would not allow the pursuit of social benefits of the medical research to modify these requirements. Investigators may not expose subjects to risks of incremental harm when performing either therapeutic or non-therapeutic procedures unless they give adequately informed consent. Unnecessary exposure of subjects to risk must be prevented. Finally, therapeutic research procedures must not be used if they provide less than optimal treatment.
A balancing approach will allow partial fulfillment of the protective conditions if it is necessary to achieve research objectives and if the well-being of subjects is not significantly compromised.

When the protective conditions are breached, the subject-oriented as opposed to the balancing approach have very different practical implications:

1. Breach of the condition that only consenting subjects be exposed to incremental risk.

Such a situation would arise if repeated blood tests were to be done on the children of mothers who were given the HIV vaccine during pregnancy, hypothetically speaking.

Using a subject-oriented view, the use of "minimal- risk", non-therapeutic procedures is permissible because they create no incremental risks for non-consenting subjects. "Minimal risk" is defined as the probability and magnitude of harm that is "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests". In the above instance, the blood tests would be permitted. If, however, the children had to have bone marrow aspirates, this would not be permissible as it would constitute more than minimal risk.

Using a balancing approach, on the other hand, non-therapeutic procedures involving more than minimal risk may be used only if there is a minor increase over minimal risk and the interventions are likely to be familiar to children with the disorder being studied. In addition, the study must be necessary to produce knowledge about the subject's disorder that is vitally important.
Hence it is clear that where subjects are unable to consent, the rules are extremely strict, even if the balancing approach is used.

2. Breach of the condition that the harms that subjects will be exposed to will be minimised.

This situation would arise if it were decided that South African subjects would be used to test a vaccine made from a viral subtype that does not occur in South Africa (Soal 1998: 17).
The acceptability of this study could be challenged on two grounds. Firstly, the subject-oriented view would have a strict requirement for consent to such risk. This approach would question why a prospective subject would willingly and knowingly consent to a risky trial that is unlikely to benefit South Africans. A proponent of the subject-oriented approach might insist that an appropriate vaccine made of a local viral subtype be used to avoid exposing subjects to any unnecessary and inappropriate risk.

The balancing approach, by contrast, might see the risk as reasonable if benefit accrues to humanity, in general, in another part of the world where the particular viral subtype is

common. Also, the possibility of cross-clade reactivity across different subtypes has not been tested and might work, conferring benefit to South Africans as well. The protective condition of the harm-benefit ratio might be waived in this instance in view of the anticipated benefit to society.

3. Breach of the condition that investigators not provide less than optimal treatment when providing therapy in the research setting

This particular problem cannot be applied to the proposed vaccine trials as there are no equivalent or optimal vaccine options at present. Also, the vaccine is a prophylactic rather than a therapeutic modality and there is no data available yet on the optimal vaccine. If, however, more than one vaccine option becomes available, the subject-oriented view would require that the physician inform the patient of which treatment alternative offers the most favorable risk-benefit ratio for the patient. This suggests that physicians who believe that the treatment arms of a randomised clinical trial are not equally favorable should not recommend participation to their patients. This has serious implications for placebo controlled trials because participants run the risk of no treatment during their participation in the trial. A subject-oriented view in this regard would favor non-participation. This would seriously retard the progress of scientific research.

Use of a balancing strategy may lead to less stringent conditions for involvement of subjects in randomized clinical trials. Requiring physicians to make treatment recommendations can seriously impair efforts to accrue enough subjects who accept randomization, because they are more likely to want the treatment preferred by their physician. Furthermore, withholding a treatment recommendation will not significantly compromise the welfare of subjects, because randomized clinical trials are not justified unless investigators can honestly state that there is no scientifically validated reason for preferring one of the treatments being compared. Thus, a balancing approach may allow investigators to seek participation of subjects in the randomized clinical trial without sharing their treatment preferences.

Problems Related to Fair Treatment

Medical research is a cooperative social endeavour subject to the requirements of distributive justice. In order to ensure equal opportunity, some classes of subjects may have to be treated differently from others in the distribution of protective mechanisms. Subject-oriented and balancing approaches will assign different weight to fair treatment in the conduct of research. These contrasting approaches will lead to different conclusions on a variety of justice-related issues.

1. Do economically disadvantaged subjects need special protections to prevent constraints on autonomous choice caused by undue inducement?

This issue has been raised in the context of proposed vaccine trials in Africa where economically-disadvantaged people might be offered inducements to participate, such as a health care plan or monetary payment.
A subject-oriented approach would require that economically indigent persons should be provided with stronger protections because they are especially vulnerable to monetary inducements. This might entail reducing the amount of compensation offered or using more economically advantaged research participants.
A balancing strategy might permit the use of incentives if it is necessary to achieve research objectives and the subjects' welfare is not significantly compromised.

2. Should injured research subjects be compensated?

In the context of the HIV vaccine trials this issue relates to whether subjects who develop HIV/AIDS should receive anti-retroviral treatment or not.
A subject-oriented view involves the straightforward application of the notion of fair treatment. According to Ackerman and Strong, harms incurred by research subjects are burdens resulting from participation in a cooperative social endeavour. Subjects who develop HIV/AIDS will be less able to pursue their life plans than non-affected subjects.

Provision of treatment constitutes a useful mechanism for redressing the inequality caused by their illness. This approach favors the treatment of those who develop HIV/AIDS during the course of the trials.

On the other hand, the balancing approach questions the appropriateness of compensation for harm sustained in the course of research. The cost of such an exercise might drain already limited research funds. Retroviral treatment is exorbitantly expensive, especially if state of the art triple therapy is provided. Furthermore, proponents of this approach feel that the risk of harm is offset by the special advantages associated with participation in research - the treatment being evaluated often represents the best option for dealing with a life-threatening illness; nursing care is often more intensive and specialised in the research setting and the research centre often provides access to a variety of specialists and services for diagnosis, monitoring and rehabilitation. In this event, even if a subject sustains harm from a research procedure, it may have constituted the option of treatment with the best harm-benefit ratio. The balancing approach might compensate harms caused by non-therapeutic interventions but not harms due to therapeutic interventions.

Society, Subjects and Medical Research

It is abundantly clear from the preceding discussion that the subject-oriented and the balancing approaches yield completely different and often opposing conclusions regarding the moral restrictions that should circumscribe the conduct of medical research. Ackerman and Strong go on to show how these two approaches represent profoundly different views regarding the role of society in research, the expectations placed on its members and the importance of medical research as a societal venture (Ackerman and Strong 1989: 166-179).

The subject-oriented approach reflects three basic assumptions:

1. The basic role of society is to implement norms of behavior that protect its members from violation of their moral interests by other persons.

2. Society can expect of its members that they will observe these basic rules for protecting the moral interests of each person but society should not require that its members participate in any particular kinds of social activities.
3. Medical research is not ordinarily essential to the preservation of society.

From these basic assumptions, it can be concluded that the benefits of medical research should be treated by society as highly desirable but morally optional. As such, society should not require participation of its members in research.

A balancing view starts from a very different set of assumptions:

1. Society has the general function of providing the essential conditions its members need to pursue their life plans. These conditions include protection against exploitation by others, but also involve the provision of the essential goods people must have to pursue their life plans, like housing, nutrition, education and health care.
2. The provision of essential resources to all members of society can only be secured through social co-operation. Hence, all individuals are expected to assist in their production. Constraints on the moral interests of individuals may be necessary in order to provide all persons with essential goods.
3. The essential resources persons need to pursue their life plans include adequate health care. Medical research contributes to the growth of medical knowledge. Hence, medical research is an essential component in providing adequate medical care to the members of society.

These assumptions suggest a different approach to the use of human subjects - society should formally sponsor clinical investigation and society should set expectations for the involvement of its members in clinical research.

The choice between these two conflicting approaches in the use of human subjects will reflect the moral significance of vulnerability, interdependence and sociability in human relationships.

Vulnerability:

Here we look at the extent to which persons misuse those who are more vulnerable than themselves. The Tuskegee Syphilis Study provides an excellent illustration of this phenomenon. Where the chance of researchers exploiting subjects is great, over-riding weight is given to the subject-oriented approach. If, on the other hand, researchers will modify protective conditions with sensitivity and responsibility, a balancing approach would be favored.

Interdependence:

The perceived dependency of persons on one another for basic goods and resources is another important factor. If many persons are highly dependent on others for goods or resources, a balancing approach would be favored. If, conversely, persons are confident to pursue their life plans independently, provided with basic protections for their moral interests, then a subject-oriented view is preferable.

Sociability:

This factor examines the compatibility between the values and interests of particular individuals and the needs of other members of society. If it is felt that the needs of individuals may diverge from the needs of other members of society, a subject-oriented view would be chosen to protect the values and interests of each person. However, if some interest in the general welfare of others is considered essential to the personal fulfillment of each individual, a balancing approach would be preferable (Ackerman and Strong 1989: 166- 179).

Ultimately, these two conflicting approaches have their origins in two broad based theories in ethics - liberal individualism as opposed to a form of moderate communitarianism and this opposition will be examined in the next section.

7. Trial Participation - the tension between liberalism and communitarianism

The review of the subject-oriented view as opposed to the balancing approach clearly indicates that the subject-oriented view is in keeping with the ethos of Liberal Individualism. Protective conditions for consent, the risk of harm and the fair treatment of subjects cannot be waived.

According to Ackerman and Strong, the subject-oriented view is a dominant approach in the context of exploitation of the poor and vulnerable. In South Africa, as we emerge from a history where the rights of the vulnerable and poor have been negated in the service of apartheid, the preference for a subject-oriented view, where research is concerned, is a logical choice. Our new democratic order, our Constitution and Bill of Rights bear testimony to this. Liberal Individualism has reached South Africa also!

This is the liberal democracy that Fukuyama sees as "the endpoint of mankind's ideological evolution", the "final form of human government" and as such, the "end of history" – where history is seen as a single, coherent, evolutionary process – in a Hegelian tradition. In this tradition, the "evolution of human societies was not open-ended, but would end when mankind had achieved a form of society that satisfied its deepest and most fundamental longings". As such, there would be "no further progress in the development of underlying principles and institutions, because all the really big questions had been settled" (Fukuyama 1992: xi-xxiii).

Fukuyama believes that the greater part of humanity will be led to liberal democracy – for two reasons. Firstly, it results in a stable economy and secondly, it provides an answer to the "struggle for recognition".

Economically, liberal principles like the free market have "spread and succeeded in producing unprecedented levels of material prosperity, both in industrially developed countries and in countries that had been....part of the impoverished Third World".

However, Fukuyama finds economic interpretations of history incomplete and unsatisfying, because "man is not simply an economic animal". For the sake of completeness, we need to examine man's "struggle for recognition".

This struggle for recognition is based on man's need to be "recognised as a human being.... as a being with a certain worth or dignity". Of the three parts of the soul described by Plato - the desiring part, the reasoning part and thymos or spiritedness – the propensity for self-esteem arises from thymos. Fukuyama describes it as an "innate human sense of justice". Humans believe that they have a certain worth. When this is negated, they become angry; when this is reinforced, they feel pride. It is this thymos which ultimately drives the historical process.

Liberal democracy - according to Fukuyama – replaces the irrational desire to be recognised as greater than others with a rational desire to be recognised as equal. However, critics of liberal democracy believe that the universal recognition is incomplete because capitalism creates economic inequality. Hence, liberal democracy "recognises equal people unequally". Is liberal democracy then not "prey to serious internal contradictions, contradictions so serious that they will eventually undermine it as a political system"? (Fukuyama 1992).

In the discussion of ethical issues related to research in the Third World, we have seen many such internal contradictions in the theory of Liberal Individualism. Most striking is the fact that a strict adherence to a subject oriented approach ultimately renders research impossible and this will ultimately lead to the decline of the individual!

In South Africa, a tension exists between the new democracy and the old tradition of communalism or Ubuntu even though the latter exists in a much diluted form due to the spread of liberal individualism.

Unlike the subject oriented approach, the balancing approach is more closely aligned to a sense of society or community – medical research is seen as one of the essential goods in a society and is therefore vital to the survival of such a society.

Christakis comments that an African might find it "difficult to see how the interests of the subject conflict with the interests of the society except, of course, if the society is not his own". In traditional Africa, the interest of the subject and of society are necessarily congruent.

This is in keeping with the Nguni belief that "umuntu ngumuntu ngabantu" – a person is a person through persons. Each individual member of the community sees the community as themselves, as one with them in character and identity. There is no room for a separation between the individual and the community. People see themselves as "potential persons" who become fully human to the extent that they are included in relationships with others (Shutte – unpublished data).

Alasdair MacIntyre, using somewhat different concepts describes a similar connectedness to the community when he describes a virtue-based morality for life in the post-Enlightenment period. Much of this results from his disillusionment with the Enlightenment project in general and with Enlightenment morality, in particular, which he sees as non-existent. In his account of a "unitary core concept of the virtues" he describes a "practice", the "narrative order of a single human life" and he situates these in the context of "a moral tradition". The third stage is essential because "we are all bearers of tradition, we function within, and gain our social identity through membership in communities. Against the type of modern theory of individualism which speaks as if each of us is a separate and discrete individual...,MacIntyre is helpful in reminding us of our historical situatedness and social identities" (Bernstein 1982: 115-140).

Ultimately, the dilemma we face in the HIV Vaccine Trials is one of modernism, where universality and individualism are stressed, as opposed to postmodernism, where particularity and community or context is a dominant feature.

8. Trial Participation - Ubuntu, our only hope, or Ethical Relativism ?

There is no doubt that Africa, and South Africa, in particular, is an ideal site for HIV vaccine research in view of the HIV/AIDS epidemic we are currently experiencing. We have seen that the HIV Vaccine Trials pose a grave and significant risk to the individual who may subsequently have little to gain. Under such circumstances, statistically significant trial participation can only be ensured by an appeal to altruism, in the African context, Ubuntu. In this regard, the interests of science and society are seen as one with the interests of the individual. Interdependence and connectedness is a prominent feature of traditional African society. In such a setting, trial participation and hence medical research will be possible.

However, with the influence of Western Liberalism, an appeal to Ubuntu is not going to be easy. The principle of autonomy is becoming slowly but firmly entrenched in Africa. A retreat to Ubuntu will be seen for what it is - a convenient retreat to a comfort zone to suit the whims and fancies of Western researchers.

It would appear that the West has realized that their very own concept of liberal individualism, which has generally worked well for them, is becoming problematic as a result of its spread to Africa. Having developed a strong sense of self-preservation in keeping with the ethos of liberal individualism, it appears as if they want to retreat from their universal principles of equality and liberty to "different", local standards of care. This can only be achieved if some of the" rules" are changed and the World Medical Association is taking the lead in attempting to amend the Declaration of Helsinki.

The draft revisions of the Declaration of Helsinki, in particular, section18, qualify the insistence that all participants, including controls, be 'assured of the best proven diagnostic and therapeutic method' by adding the rider that such interventions only refer to those 'that would otherwise be available to him or her'. In other words, the ideal of a

universal 'gold standard' of treatment would be abandoned in favour of a standard dependent on local conditions (London 1999: 812-813).

As a result, in terms of the HIV Vaccine Trials, participants who develop HIV/AIDS in the course of the trials will not be treated with anti-retroviral drugs as this would otherwise not be available to him or her in South Africa. This would represent an enormous saving to multinational drug companies involved in vaccine research as they potentially have the most to gain from such vaccine trials, especially if they are conducted cheaply in Africa.

The proposed revisions to the Declaration of Helsinki reek of ethical relativism. Such relativism threatens to "institutionalise global injustice in the application of ethical standards" (London 1999: 812).

The core of the ethical dilemma now confronting the 'West', as it attempts to realise its domestic and global agendas around the world, is one of cultural conflict. The Western concept of liberal individualism (amongst others) conflicts head-on with Confucian, Cantonese, Hindu, Bhuddist, African, Islamic, and other cultural influences that dominate globally (67% of the global population is non-Christian). For example, the Chinese, who number 1,254 billion people and form the largest cultural group on the planet (World Population Data Sheet 1999) have their own system of ethics. For 2500 years Confucian ethics was the dominant moral philosophy and ideology of Chinese culture. Ancient Chinese medical ethics is based on Confucian ethics. It has strong deontological features and is virtue-based. Humaneness forms the core of its principles (Tsai 1999: 316-317). The community and family take precedence over the individual in such dominant and mature value systems worldwide.

The West has recognised this, and is now attempting to make its global 'missionary' efforts more effective by mutating Western concepts like liberal individualism, and others, to form hybrid concepts that are more palatable to the "heathens", as a means to

realising Western agenda's anyway! It is not surprising that this often results in human rights abuses in the first and third world alike.

In rural Africa, an appeal to Ubuntu could succeed in harnessing trial participation. However, in the developed areas of Africa, where individualism is spreading, this might not be possible.

9. Conclusion

As anticipated, participation in the proposed HIV Vaccine Trials in South Africa will be riddled with ethical concerns. The area expected to be most problematic relates to respect for autonomy and informed consent. In South Africa, this process will not always involve the individual but significant others may also be consulted by trial participants. Information will have to be presented in a culturally relevant form and written information and consent will be problematic in the context of high rates of illiteracy. Voluntariness must be preserved when dealing with vulnerable populations and the use of extraordinary incentives will certainly constitute undue influence. Finally, in this regard, competence becomes questionable when significant understanding of complex scientific details is required of people who are educationally disadvantaged.

In preserving the principles of beneficence and non-maleficence, the risks to potential trial participants, both medical and social, outweigh the perceived benefits. Any benefit to be gained will be gained by high- risk participants only or if benefit to the individual is combined with societal benefit and then weighed against risk. The high risk profile of these trials would negate the principle of justice if the possible benefits of the trial in the form of a free or subsidised vaccine were not made available to the people who volunteered to bear the burdens of this research. Similarly, if participants developed HIV infection in the course of the trials and were not given treatment, the principle of justice would also be violated.

If the principles in which the Declaration of Helsinki is grounded are strictly adhered to, a subject-oriented approach would be favoured. Constraints on the rights of the individual will be impermissible and in the Third World, this would render research unethical and hence, impossible. Conversely, many of the world's dominant cultures allow infringements on the rights of the individual to produce societal good. This, coupled with a limitation on the risk to the individual, constitutes a balancing approach which sees research as an essential requirement for the survival of all of mankind.

Hence, it is evident that it is problematic to pursue an individualistic view, perhaps in general, but especially where research in the Third World is concerned.
This does not imply that the ethical guidelines which already exist and which protect the interests of research subjects should be abandoned. Nor should one aim for universality of existing Western principles because the global population is not homogenous and universality "obscures and obliterates the particularity and specificity of morality which is grounded in communal traditions"(Bernstein 1981). For example, if autonomy is to be viewed as a truly universal principle, is it not possible that the "North American paradigm is only one version of it"? It is therefore unnecessary for "every country to follow the practice of autonomy in all of its details in a fashion identical to that found in North America" (Akabayashi 1999: 299).

The Four Principles Approach provides a valid framework in which to consider the various ethical issues but, as a Western construct, does not "take into account local customs and traditions that should be respected and incorporated into the research process" as far as is possible (Loue 1996: 51). So, although incomplete, it is not incompatible with values in other cultures. Compared with Ancient Chinese medical ethics, there is considerable overlap except where autonomy is concerned (Tsai 1999: 316-317).

As such, culturally relevant ethical issues need to be incorporated into existing frameworks to augment them with cultural sensitivity. However, changing the rules from time to time and from place to place to achieve the research aims of the West will be both unjustifiable and morally reprehensible. Furthermore, fulfilling the additional requirements will be time-consuming, whether this takes the form of massive education campaigns to reduce educational inequalities between first and third world communities or additional time for consultation with family prior to providing informed consent. While this may also be costly in economic terms, Western researchers and multinational drug companies will have to realise that they too have a responsibility in reducing the inequities between first world and third world communities.

Undoubtedly, the HIV Vaccine Trials in South Africa will pose a major ethical challenge to all involved. We must, however, be wary that in our haste to develop and test an HIV vaccine, we do not cause an ethical catastrophe that we will never be able to justify. It has taken a long time for the research community to recover from Tuskegee. May we never tread along that path again!

Ultimately, the dilemma we face is the application of "Modern" ethical principles and theories to a "Postmodern" world. Unlike the objectivity, universality, rationality and individualism emphasized in Modern or Enlightenment ethics, the postmodern period in which we live demands subjectivity, particularity, sensitivity to context, cultural tolerance and positive deconstruction of existing norms. It is only by embracing a postmodern approach and by taking what is good out of modernity that medical researchers, globally, will enter the new millennium to meet the ethical challenges which lie ahead, with integrity and moral responsibility.

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