

CLINICAL TRIALS IN SOUTH AFRICA

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Due to the cost of developing biopharmaceutical products, and problems with adequate subject recruitment for clinical trials in the United States and Western Europe, outsourcing clinical research in newly emerging regions is increasingly common. Although the most dominant emerging regions are primarily countries in Latin America, Central and Eastern Europe, and Asia, some countries in Africa are also becoming prominent locations for clinical research. Past concerns about inadequate infrastructure and socio-political-economic problems in many parts of Africa have impeded growth in clinical research in the past. However, changing requirements such as patient diversity and the need for greater subject numbers in clinical trials in parallel with improved clinical research environments in some African countries, such as South Africa, have resulted in notable growth in clinical research in the region.

Why South Africa?

Two things distinguish South Africa from other countries in Africa: South Africa is the most economically developed African country and it has established better regulatory standards for conducting clinical trials. However, several factors are responsible for the growth of clinical research in this country. Firstly, South Africa's total population is nearly 48 million which provides a large, diverse patient population. Secondly, the majority of subjects enrolled in clinical trials have not received any previous treatment for their disease either because it is not available to them or they cannot otherwise afford it. These factors greatly facilitate subject recruitment and help meet diversity requirements. In addition, lower costs for clinical research and lower risk of litigation make South Africa attractive for foreign companies outsourcing clinical trials.

Although clinical research has been established in South Africa for a number of years, from 1997 to 1998 there was a 40% increase in total clinical trial activity (Christley 1998), due primarily to highly effective recruitment and retention rates. Recently, the most significant growth in clinical research has occurred in disease areas prominent in South Africa including HIV/AIDS, TB, malaria, cancer, and diabetes. In addition, multi-site trials in HIV, dermatology, hematology, asthma, chronic bronchitis, and pediatric and adult pain studies are becoming increasingly common. The number of clinical trials conducted in South Africa has been

growing exponentially over the last couple of decades across a wide range of therapeutic areas. According to the Beare Pharmaceutical Industry Report on South Africa in the year 2001, approximately 400 studies were conducted. This number has continued to grow due to the highly successful recruitment rates among patient populations and an improved regulatory environment. Despite South Africa's satisfactory clinical research environment, there are many vulnerable populations that live in great poverty and have little access to any medical care. Many of these individuals are poorly educated and tend to accept authority without question. This raises ethical issues when obtaining informed consent. In addition, it is not surprising that the focus on clinical research has been on infectious diseases, particularly HIV/AIDS, TB, and malaria, as large numbers of the country's population are greatly affected by these diseases. However, because many are extremely vulnerable, such as the large numbers of HIV pediatric cases (see below), improved regulatory measures to protect these individuals must be implemented.

Furthermore, language and cultural differences between ethnic/racial groups contribute additional barriers that must be taken into account. Taking greater measures to maintain international ethical standards particularly among vulnerable populations in South Africa will help pave the way for improved clinical research in other African countries.

HIV/AIDS: HIV epidemiology and clinical studies are especially prevalent in South Africa, due to the growing epidemic of HIV/AIDS. At the end of 2007, 5.7 million people were living with HIV/AIDS in South Africa (UNAIDS 2008 report on the global AIDS epidemic) one of the worst AIDS epidemics in the world. As a result of these alarming statistics, in 2000 the South African government implemented an HIV Vaccine Action Campaign in an attempt to control the epidemic. Currently, sixty percent of the world's HIV/AIDS infected people are in Africa, and 59% of all infected individuals are women (Global Campaign for Microbicides in Africa 2006). Because of the high incidence of mother to child transmission, as of September 2008, South Africa's Minister of Health announced a full-fledged commitment to the prevention of HIV transmission to children.

The first large-scale study to evaluate a candidate HIV vaccine on the African continent was recently announced by study collaborators in the United States and South Africa. The trial involves up to 3,000 participants at five sites throughout South Africa and is expected to continue for four years (Fred Hutchinson Cancer Research Center 2007). In previous phase I and II trials this vaccine was found to be safe and effective against HIV in more than half of the subjects tested. There is much hope that a safer and more effective vaccine will help control the exponential growth of this terrible epidemic.

After eight years of research, one South African developed HIV vaccine is to become the first African vaccine to undergo human clinical trials in the United States (South Africa: The Good News 2008). Results could take between five to eight years; however, the accomplishment of an undeveloped nation such as South Africa to develop a candidate vaccine and undergo clinical trials is already

a milestone. If successful, the impact on the HIV/AIDS epidemic in Africa could be very significant.

Tuberculosis (TB): In 2006, the World Health Organization ranked South Africa fifth among the world's 22 countries most burdened by TB. The incidence of TB has increased significantly in South Africa in parallel with the HIV/AIDS epidemic. According to the 2006 USAID Infectious Diseases Report on South Africa, up to 60 percent of adult TB patients are HIV-positive. Furthermore, TB is one of the principal causes of HIV-associated deaths among HIV patients. However, since the emergence of the HIV epidemic, the directly observed therapy strategy known as DOTS has failed to contain the spread of TB, particularly in southern Africa. Furthermore, progress in developing a treatment against multi-drug resistant strains has been relatively slow. In order to conduct large scale Phase III TB vaccine trials and improve the infrastructure for clinical research in South Africa, in 2007 Denmark's Medicon (in collaboration with Aeras Global TB Vaccine Foundation) trained 9,000 South Africans in clinical research methods. This effort has facilitated clinical research in South Africa in all therapeutic areas (Ministry of Foreign Affairs of Denmark 2006).

Out of the several potential TB vaccines being developed for clinical trials, one candidate is currently undergoing Phase II trials in South Africa. This particular vaccine is the most advanced of a new generation of preventive TB vaccines, and is being tested in a Phase IIb proof-of-concept trial at the University of Cape Town. The vaccine will be given to children who have been immunized with the BCG vaccine at birth in order to improve the level of immune protection. This is the first proof-of-concept trial of a new preventive TB vaccine in infants after many years and is part of an effort by the South African Tuberculosis Vaccine Initiative (Wellcome Trust 2009).

Malaria: Malaria is endemic in the low-altitude areas of the northern and eastern parts of South Africa with seasonal transmission. The renewed increase in the incidence of malaria was a result of a worldwide ban on DDT in the 1970s. Attempts to develop a vaccine which prevents infection have been unsuccessful as yet, although there has been considerable progress over the last 25 years. Approximately ninety percent of malaria-related deaths occur in sub-Saharan Africa, and the majority of malaria casualties are children under five. Because malaria infection in Africa can be fatal, the incentive for developing a successful vaccine that provides long-lasting immunity is great.

The final phase of testing for "the world's most advanced malaria vaccine candidate" was recently initiated with five infants from Tanzania. Over the next few months, 16,000 children under the age of two will receive this malaria vaccine in several African countries including South Africa. The successful completion of a Phase III trial would make the vaccine available possibly by 2012 (OneWorld US 2009). A safe and effective children's vaccine for malaria prevention would greatly reduce malaria infection in South Africa where according to the WHO most of the one million people killed by malaria are less than five years old (OneWorld US 2009).

Regulatory Approval and Ethics Review: South Africa's relatively well-developed infrastructure and compliance to ICH-GCP guidelines are two factors that have contributed to the country's growth in clinical research relative to other countries in Africa. In 2000, a South African Good Clinical Practice (GCP) guideline was published by the South African Department of Health; a stricter version that strengthened the existing requirements was later published in 2006. Despite the fact that approval processes are somewhat lengthy, currently averaging twelve to fourteen weeks, review and approval by the Medicines Control Council (MCC) responsible for scientific, medical, and ethical issues relating to clinical trial applications in South Africa, is fairly consistent (see MCC website <http://www.mccza.com>). Other related agencies include the non-profit organization South African Clinical Research Association (SACRA) and the local Industry/Regulatory Task Group (IRTG).

In 2001, the World Health Organization Regional Committee for Africa expressed concern that some health-related studies undertaken in the region were not subjected to any form of ethics review (Weiss 2001). There are several examples of ethically compromised clinical studies that have been conducted in South Africa in the past. One such study is a breast cancer study conducted by Werner Bezwoda, a white oncology/hematology professor, on black women at Baragwanath hospital in South Africa in 1995. A review revealed that no patient consent or ethics review were provided during the course of the trial (Weiss 2001). Although some past studies have not met adequately with international standards, more recent legislative changes have been put into place. In addition to the requirement for ethical standards, there are additional requirements specific to conducting clinical trials in South Africa.

In 2005, the Department of Health released a national guideline outlining ethics in health research in South Africa requiring that Ethics Committees be "representative of the communities they serve and increasingly reflect the demographic profile of the population of South Africa..." These guidelines, similar in principle to the International Conference on Harmonization for Good Clinical Practice guidelines (ICH GCP), specify in greater detail the requirements for diversity, demographic representation, and occupational identity specific to South Africa (Moodley and Myer 2007).

Informed Consent

The issue of ethical informed consent practices in South Africa is a controversial one. Limited education, poverty, inadequate protection of human rights, discrimination on the basis of health status, and limited access to preventive care and treatment options are all contributing factors. Although there are significant improvements in the quality of clinical research conducted in South Africa, particularly involving ethical considerations, there are certain important aspects of the population which must be taken into account. These include political and socio-economic factors, illiteracy, language barriers, and cultural differences among patient populations.

Political and socio-economic factors: South Africa is a middle income country with severe economic disparities. The majority of the population is categorized as socio-economically low status and 50% of South Africans live below the poverty line (CIA World Fact Book 2005). Almost two decades after the end of apartheid, vast racial inequalities still exist. Many South Africans continue to be underserved and disadvantaged because of their race and/or ethnicity, especially regarding healthcare (Kon and Lackan 2008). An awareness of these issues is vital to maintaining the standards appropriate for international research. Vigilance on the part of sponsors to ensure that past prejudices do not interfere with current studies is crucial.

Illiteracy: Recently a new “speaking book” has been developed to help inform less- educated subjects of the benefits and risk factors involved in clinical trial participation. Approximately 4,500 of these books are to be distributed in four Sub-Saharan countries, including South Africa, before the end of 2008. The advantage of these speaking books over conventional methods is that the books provide a verbal explanation accompanied by visuals rather than a written text. (Kloiber and Duncan 2008). Considering the illiteracy rate among much of the clinical trial participants in South Africa, this new method will greatly improve subject understanding and help raise ethical standards. Although the reported literacy rate among adults in South Africa is 86%, this rate varies significantly among different ethnic/racial populations (CIA World Fact Book 2005).

Ethnic/Racial Groups: (CIA World Fact Book Statistics 2005)

African 79%

This population consists of several groups including Khoi-San, Xhosa, Zulu, Ndebele, Sotho, Shangaan and Venda. Among these, the biggest groups are the Zulus (21 %), the Xhosas (17 %) and the Sotho (15%).

Africaans 9.6%

The Africaans are primarily descendants of Dutch, French, English, and German settlers who arrived in the late 17th century. They are called Afrikaners and speak Afrikaans, a language closely related to Dutch.

Mixed Race 8.9%

Among the non-Africaans, the second largest group in South Africa is of “mixed race” or Africaans who are mixed with other ethnic/racial groups including Indians, Malays, and Africans, most of who (89%) live in the Cape Colony.

Indian/Asian 2.5%

The largest Asian group is made up of Indians. About one million Indians live in South Africa, 80% of who live in the Natal province. The majority of Indians were brought by the British in the 19th century. They continue to speak their own native languages and follow many of their native Indian traditions.

Although the separation of these groups is gradually lessening following the end of the apartheid government, there continue to be significant linguistic and cultural differences among them. These differences must be taken into account in how they affect clinical research.

Language Barriers: There are eleven official languages in South Africa, the most common of which are English and Afrikaans. Each of the eleven includes a number of regional dialects and variants. Nine of South Africa's official languages (all except Afrikaans and English) are Bantu languages. Bantu languages are a large branch of the Niger-Congo language family, which is represented throughout much of sub-Saharan Africa. Because of British rule, English is the most common language of the government, business, and scientific communities. However, according to the 2002 Pan South African Language Board survey, only 22% of the population has an adequate understanding of spoken English such as that used in political speeches. Furthermore, different regions in South Africa predominantly speak distinct languages, including Zulu, Sotho, and Afrikaans, depending on the dominant influences and ethnic groups.

Informed consent and other patient-related materials must be translated into the native language of the patient. In South Africa this is not a simple issue. Not only are there several official languages, but there are not always well-established translation equivalents for standard clinical trial terminology. For example, one South African study concluded that language may create barriers to informed consent by prospective research participants when there are no local words for 'randomization' or 'placebo'" (Abdool Karim 2000).

Cultural Differences: Informed consent concepts are interpreted differently in different parts of the world. In traditional, rural African communities for example, a form of "communitarianism" dominates (Moodley 2002)). In this context, research is an altruistic endeavor that benefits communities and societies. Western ethical consent guidelines that emphasize the individual over the community may not apply in this type of environment.

To better address informed consent issues such as language and cultural barriers, the UNAIDS guidelines for HIV vaccine research recommends a process of consultation between community representatives, researchers, sponsors, and regulatory bodies to design a more effective informed consent strategy. One example of this approach that has already been executed is an advisory board in rural Hlabisa, South Africa. The board consists of eight local people who serve as community liaisons to develop education materials, consult with and inform the community about new research projects, and provide advice to researchers about local needs for the ethical conduct of research (Shapiro and Stein 2004). These individuals possess knowledge of the local culture and language(s), and are therefore well equipped to overcome potential barriers to clinical research while ensuring that ethical standards are maintained during the process of informed consent.

Conclusions

In order to conduct responsible, successful clinical trials in South Africa, an understanding of the differences that exist among various populations, including socio-economic factors, illiteracy, and language and cultural barriers is crucial. An awareness of the limited education and medical access for many vulnerable populations is also important especially in light of past studies which have ethically compromised these subject populations. Clinical research can be beneficial for both the sponsor and the participants only when ethical international standards are maintained. Considering the large and diverse number of subjects that can be recruited for clinical trials in South Africa, it is understandably becoming an important clinical research location. However, along with testing for safe and effective therapies, the opportunity to improve the health status of many patient populations is great. In addition, the large populations devastated by infectious diseases such as HIV, TB, and malaria may greatly benefit from recent drug developments and clinical research being conducted in South Africa.

Finally, because, according to many investigators, South Africa provides a better environment for clinical trials than many other African nations, it can serve both as a model for clinical research in Africa and to help improve preventive care.

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