Advantages and Challenges Facing Clinical Research in South Africa

PEER REVIEWED

Introduction

Clinical research has a long history in South Africa and dates back as far as the 1960s. During the early years, clinical research was primarily confined to the academic university research units based at the major medical schools in the major cities of South Africa. Over the past two to three decades, as pharmaceutical research has proliferated and the need for investigator sites has grown, medical doctors - having been exposed to clinical research during their early careers - have established their own research units to fulfil this need.

South African Healthcare System

The South African healthcare system consists of public healthcare, which is financed and managed by the South African government, and private healthcare, which is primarily funded by health insurance and private direct fee for service payments. Private healthcare consumes more than 50% of total healthcare spending in South Africa, but only services about 20% of the population able to afford health insurance or direct funding of their healthcare needs.

Attraction of South Africa as Clinical Research Destination

South Africa is classified internationally as a developing country and is often viewed by the less-informed as a poorly-developed African country. This is far from the truth.

As mentioned in the introduction above, South Africa has a long history of conducting clinical research; this translates to interest of the medical profession in furthering their knowledge and remaining at the cutting edge of medical development. This is a good indication of the pool of experienced clinical research staff available for research, which is growing and developing as the research environment changes over the years. Clinical research experience is of paramount importance in the South African research environment: it is a regulatory requirement that investigators may only participate as principal investigator after having participated in at least two different clinical trials as a sub-investigator. A major attraction of running clinical trials in South Africa is the commitment and dedication of the majority of doctors and medical support staff conducting research in the country. Rarely are target numbers for eligible patients not provided for different trials. This has often resulted in many large studies with poor recruitment in first world countries seeking services provided in South Africa.

South Africa has a dual regulatory process in that any clinical trial requires both regulatory authority (Medicines Control Council) and relevant ethics approval prior to the commencement of the trial. This applies to all clinical trials using consumed investigational products. Strict guidelines for conducting clinical research are outlined in the South African National Health Act 2003. The Department of Health has published good clinical practice (GCP) guidelines to assist clinical research staff in performing research ethically, and to ensure the safety of clinical trial participants. It is a requirement that all research staff are fully trained in GCP, and updated certification is needed every three years. Ethics committee approval is also required before clinical trials can commence. There is a choice of use of central ethics committee or institutional ethics committee. The general rule of thumb is that the university/academic sites generally require the institutional ethics committee to review and approve the trial being performed at their facilities. To ensure all ethics committees adhere to specific standards, the National Health Research Ethics Council (NHREC) was established in 2005 to regulate the standards of all ethics committees in the country.

South Africa has a sophisticated infrastructure and clinical trial support system available. Laboratory support to process and analyse blood and tissue samples is readily available in all the large metropolitan cities in South Africa. Most, if not all, of the major laboratories have a clinical trial division that specifically caters for the clinical trial environment, and usually have some partnership/working relationship with the large multinational analytical laboratories. All the clinical laboratories are audited and accredited by SANAS. These facilities meet all of the international standard requirements.

As South Africa is located quite a distance from the major manufacturing facilities in the USA, Europe and Asia, investigational product depots are often used to import and distribute clinical trial products to site. These facilities adhere to all international packaging and manufacturing (GMP) and clinical trial requirements (GCP). As they generally receive, store, and distribute clinical trial investigational product for a number of different studies and companies, they have very strict control mechanisms in place to ensure confidentiality and safety of clinical trial product. They are able to manage all types of investigational product at all temperature ranges.

As South Africa is a relatively small country in terms of size, travel distances by air and road are on the short side. All the major multinational courier services have a direct presence or partnership with local services. Once a study is approved by MCC and Ethics, the MCC approval letter serves as the import licence for the investigational product. The accompaniment of proforma invoice and transport documentation makes for relatively smooth importation of clinical trial product. The courier services have the facilities to handle temperature-sensitive investigational product without compromising the integrity of the product.

Challenges of Clinical Research in South Africa

There are many challenges that are constantly faced when doing clinical trials in South Africa. Some are not unique to South Africa.

Patient recruitment is probably the biggest risk factor for conducting clinical trials in any country or region, and is influenced by a number of factors. South Africa is a developing country with a large proportion of the population unemployed and with limited access to best medical care available. Their primary source of healthcare is via the public health system. The public health system services 80 % of the population with 50 % of the total annual healthcare expenditure. The system is overworked, understaffed, and poorly managed due to the bureaucratic red tape needed to get anything accomplished. Patient recruitment from the poorly serviced, impoverished, and often poorly educated group does, at times, result in further scrutiny due to the inherent risks of being exploited by researchers. The challenge of balancing the benefits of the patients being exposed to fewer currently marketed medications, willingness to participate due to limited treatment options, and options of receiving some form of treatment not freely available to them; versus exploitation, capturing valid data from often complicated tools from, at times, poorly educated patients, and patient compliance due to work commitments, is something that constantly needs to be reviewed and addressed with all studies undertaken in the country.

Recruiting and retaining of participants is a major challenge, specifically for long-term studies. Slow recruitment leads to longer time to market, which in turn, leads to revenue loss. Poor retention also negatively impacts on the overall evaluable data for regulatory submissions. Dropped participants must be replaced, which incurs further expenditures and time delays. Subject dropout rates are estimated to range between 15 and 40 % of enrolled participants in clinical trials[2].

Despite the largest proportion of patients being serviced in the public health system, the majority of all clinical research conducted in South Africa is done by private health investigators. The public health service patients participating in research primarily come through academic institutions. Unfortunately, due to the overworking and understaffing of the system, clinical research is confined to the major metropolitan centres, larger academic hospitals and dedicated academic research centres. Efforts to address this by the MCC have included requesting a portion of sites participating in studies to be public health sites. This has resulted in a few new public health sites with poorly set-up sites. A lot of time and effort is then spent by monitoring CROs or sponsor companies to ensure these inexperienced sites are able to deliver quality data. In essence, some cross-subsidisation of training is being done for these sites.

Community leaders play an integral part in the lives of, particularly, the lower socio-economic and poorly educated population groups in South Africa. These community leaders can determine the success of any patient recruitment/ education drive in these communities. This has been of particular importance in the many HIV/AIDS clinical trials and education programmes. Many clinical trials that did not get the support of local community leaders were unsuccessful, and vice versa. This brings up a very pertinent point, that engaging the community and considering different cultural backgrounds is important in ensuring successful research projects. This can be achieved in many ways - from grass roots interaction of the community through the community leaders, to interactive theatre/role play presentations, community radio broadcasts, meetings, and events.

Clinical trial participants are often very eager to partake in a trial, but compliance to the many required visits could potentially become an issue without considering the following points mentioned below. This is often due to[1]:

- Monetary burden:-
  Often participants have to travel a distance (using their own finances to pay for transport) or take time off work (unpaid leave) to attend follow-up visits. This issue can be overcome by offering compensation for travel and time spent for visits. Compensation for patients may typically include some combination of medical treatment and cash compensation, intended to provide for reimbursement of expenses (travel, telephone usage, missed work, babysitter, lunch etc.) but not to be so large that it would be considered perverse incentives. All medical costs that are covered by the clinical trial should be discussed in detail with the participants: this will allow the participant to see which cost is for their own, or medical aid's, account.

Being treated with respect and kept informed will help to make the overall experience of trial participation positive for all participants[2].

- Discouragement of family members, community and disease progression:-
  Family members and the community might discourage participants from going to sites for visit, and would rather they go to traditional healers in the area for assistance. If the disease progresses and the participant doesn't have a positive outcome from the visits, the other participants might become despondent and subsequently not return

to the site. Therefore, the participant needs to diligently inform of the possible outcome of their disease.

- Commute:-
  Transport compensation is of particular importance for participants who depend on public transport. Sufficient funds should be made available to cover the full fare for participant and caregiver if needed. Weather can also have an impact on participant compliance.
- Lack of information:-
  Adequate information about the treatment risks and advice on how to make the trial more comfortable and convenient need to be discussed with the participants[2].

South Africa and other Southern African countries do have a high incidence of HIV/AIDS. The challenge of determining the impact this disease may have on the study data, integrity of the study, and effect on study participants is almost always a topic of discussion during health authority and ethics committee discussions.

The highly regulated nature of clinical research and the importance of proper and fully-informed consent prior to participation in clinical trials has presented some interesting challenges in patient recruitment. This, compounded by the increased complexity of clinical trials being presented by the pharmaceutical industry, has turned the patient information leaflet and informed consent form (ICF) into a daunting document. The ICF is usually drafted by highly-educated research staff, yet the information needs to be presented in a format that can be easily understood by non-scientific participants.

Health surveillance and epidemiological data collection is poor - primarily due to a lack of sufficient staff, and poor reporting by the clinical staff to the data collection centres. The submission of incomplete and incorrect data further hampers accurate interpretation of data. Apart from major epidemic infections of HIV/AIDS and tuberculosis, the prevalence, morbidity and mortality rates are rough estimates made from data received from private disease associations/ societies/support groups, along with private sector hospital data. Due to the heavy workload of the public health sector and poor record-keeping systems, data from this sector is incomplete, inconsistent, and unreliable. As this represents a larger proportion of the population, this unreliable information has the potential to give a skewed picture of the actual disease risks facing South Africa. This could have potentially dire consequences for conducting clinical trials in inappropriate locations.

Time is always the enemy of clinical research, and the MCC approval cycle is at least three months from the time of submission to approval of the study. It is always a challenge during this process to ensure all documents, questions, and regulatory requirements are addressed to ensure approval of the study. This is not always smooth sailing. The most common issues are overload of clinical trials for review at each cycle, the limited amount of time available to discuss specific trial concerns, lack of sufficiently experienced reviewers for trials, lack of sufficient staff at the MCC to prepare trials for review, poor follow-through communication between the MCC and the rest of the industry. The biggest challenge regarding this issue is that there is no assurance that if the trial meets all requirements that approval will be granted within the three-month cycle. This is of particular importance in seasonal studies such as vaccine studies, CAP studies etc.

A challenge facing the long-term clinical trials for chronic disease conditions is the continued use of successful treatments after completion of the trial, and before the treatment is registered in the country for use.

In conclusion, despite the many challenges encountered, these are not insurmountable, and solutions to all problems can be found. Without clinical research and the voluntary participation of ordinary people, the advances in medical treatment would not have reached where it is today. That being said, improving on past success must always be one of the goals.

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Dr Gavin Leong completed his medical degree at University of Witwatersrand Medical School in Johannesburg in 1993. Clinical experience is gained in various specialities with 6 years in anaesthesiology. Dr Leong has been involved in Clinical Research since 2001 in various capacities, namely CRA, Medical Monitor and Medical Advisor for number of different companies. He joined Criterium Inc, South Africa in 2003. Dr Leong is currently the Clinical Operations Manager for Criterium South Africa with added role of Medical Monitor for designated studies.
Email: g_leong@criteriuminc.com or headtt@telkomsa.net

Karen Mallalieu started her career in the Clinical Research in 1999 at Quintiles Clindepharm as a Clinical Trial Administrator (CTA). In 2001 she joined Pharmacia South Africa as a CTA, Monitor, EDC Liaison Officer and Clinical Trial Finance Administrator. Pharmacia was acquired by Pfizer laboratories in 2003. Karen joined Criterium Inc South Africa in 2004 as a CTA and is currently Senior CRA and assistant project manager. She gained extensive experience in all aspects of clinical Research including data capture and management at Criterium headquarters in Saratoga Springs, USA.
Email: kmallalieu@criteriuminc.com