Hurdles Associated with Conducting Multinational Clinical Trials in Developing Countries such as South Africa

Clinical research, the cornerstone of evidence-based medicine[1], requires experienced investigators with appropriate training to ensure accurate and reliable data. As far back as 1979, Wyngaarden[2] identified clinical investigators as an "endangered species". In 2005, Ley[3] reported that in the United States (US) the number of physicians engaged in patient care had increased from 1985 to 2003, while the percentage of physicians engaged in clinical research during the same time period decreased from 4.6 % to 1.8 %. The situation does not appear to be improving; new data show that the number of principal investigators has dropped 11 % globally, and 20 % in the US[4]. Of greater concern is the high turnover rate of investigators; only 27 % of clinical researchers who registered as a principal investigator (PI) in 2000 had acted as a PI in another trial by 2004[5]. The current investigator pool is also getting older, with the average age increasing from 43 to 50 years[5].

From a South African perspective, the lack of capacity for health research and the lack of researchers is equally distressing. Medical schools and universities traditionally focus on clinical medicine rather than research and this, together with the lack of governmental research funding, means that potential investigators have no alternative but to rely on funding from international pharmaceutical companies[6]. The motivation of young people to pursue a career path in research has declined, and those that do, invariably move abroad where their efforts are better rewarded financially[5,6,7].

The success of a clinical trial is dependent on the investigator[8]. Difficulties arise when clinicians invited to participate as principal investigators decline the invitation. The decision is not usually that "doctors simply don't want to take part in clinical trials"[9]. On the contrary, a number of studies report that clinicians would be eager to participate if an adequate trial infrastructure and environment was present[10-13]. There is a perception that trials involve extra work and added administrative burden. This belief is shared by Getz, who reports that it is mainly younger investigators who leave the field as they found "conducting a clinical trial is much harder than they had expected"[5].

South Africa is considered a clinical research "hot spot" due to its diverse genetic, drug-naive patient population[15]. It is known for supplying high-quality data across all phases of drug development at affordable rates[16]. South Africa has a sound infrastructure and huge potential, but it is clear that the drug industry, universities and other policy-makers need to develop incentives and training opportunities to entice medical students and physicians back into the research field[5]. To do this, it is necessary to have a clear understanding of the hurdles and obstacles associated with conducting clinical trials within a South African context.

Feasibility Process

The trial process begins by completing a confidentiality agreement and feasibility questionnaire[17]. For sponsors, clinical trial feasibilities assist in identifying potential challenges with a protocol, and provide input on how to work efficiently with different countries and sites with their respective challenges. For the researcher, however, this process is plagued with obstacles[18]. It is a time-consuming and repetitive process which often results in completion of the same feasibility for different contract research organisations (CROs).

The complexity of these feasibility questionnaires means that it is often difficult to predict potential participant numbers[18] - especially in dedicated trial units which are skilled at recruiting trial participants from numerous sources as per the protocol needs, but rarely have their own patient populations. Investigators are often forced to estimate potential participant numbers, and risk overestimating recruitment potential in an effort to ensure that they get awarded the trial. This is evident by the fact that 11 % of sites in a given trial typically fail to enroll a single patient, while 37 % under-enroll; only 39 % of sites meet their enrolment targets, and 13 % exceed them[19].

In South Africa, only 26.8 % of feasibilities result in an actual trial being awarded to a site, with the success rate being significantly higher amongst questionnaires distributed by pharmaceutical sponsors compared to CROs[18]. As a result, an investigator completes each and every feasibility questionnaire presented to him/her, and this can potentially result in competing studies being awarded. The planning process is further complicated by the difficulty in predicting time from completion of the feasibility questionnaire until first patient recruited. In South Africa, the mean lag time is 12.9 months (range 2.7 to 33.5 months)[18]. This can impact on budgeting and site staffing.

Increasing Complexity of Clinical Trials

Getz (2010) demonstrated that from 2000-2003 to 2004-2007, there has been a 49 % increase in the median number of procedures per trial, with a concurrent 54 % increase in effort required to carry out procedures[20]. This raises the issue of whether these additional procedures are essential for the trial conduct. An example is the current emphasis in clinical protocols on blood pressure (BP) measurement. An analysis of 16 multinational, pharmaceutical-sponsored, clinical research protocols concurrently being conducted at TREAD Research, a predominant cardiovascular unit in the Western Cape, South Africa, revealed five different methodologies for measuring BP. In none of these trials was hypertension mentioned as either an indication and/or primary objective (unpublished data). Getz estimates that 15 % to 30 % of data collected during the average clinical trial process is never used in a new drug application[21].

This increased complexity has placed a greater demand for qualified, trained staff, but this is hindered by the absence of certified training programmes. Good clinical practice (GCP) training remains the main training available to site staff, and in South Africa, there is mandatory GCP training with three yearly updates. However, there is neither formal GCP accreditation nor a standardised core curriculum – although steps have recently been taken to resolve this issue. Consequently, few staff members receive any formal training in research; Duane (2007) reports that as many as 75 % of study coordinators do not have any formal training[22]. Many of the staff members are thus being

trained on-site – often by inexperienced site members.

Patient Selection
The number of eligibility criteria increased from 2000-2003 to 2004-2007 by 58 % (that is, from 31 to 49)[23]. Finding suitable trial participants is thus increasingly more difficult, and is further complicated by the fact that these criteria are not consistent with disease profiles and/or with clinical/ethical guidelines. For instance, numerous type 2 diabetes mellitus trials restrict body mass index (BMI) to ≤35 kg/m^2 - yet the majority of type 2 diabetic have BMIs greater than this.

The increased number of eligibility criteria is resulting in higher screen failure rates. However, it has become common practice for sponsors to reduce the number of paid screen failure patients – often below the expected screen failure rate for the study. In addition, the payment for screen failure visits is also frequently reduced – even though the site has to spend extra time, effort and resources on these patients, as the reason for screen failure frequently requires that additional treatment and/or referral is forthcoming. This puts additional pressure on units and requires them to conduct more prescreening activities, often at their own expense.

Protocols requiring background therapy can also be challenging – especially in developing countries where prescribing practices are often dictated by financial constraints. Not only can the choice and dose of background therapy be problematic, so too can the issue of who is responsible for payment thereof. For example, many lipid-lowering studies require patients to be on a maximum tolerated dose of statin, however local guidelines dictate that considerably lower levels be used. Do these patients not get included in the study … or do the investigative sites up-titrate these patients irrespective of local guidelines … and if so, who pays for this additional medication?

Competing Trials
The drug development pipeline is such that many companies are researching the same compounds, with the result that units are often approached simultaneously with similar protocols. Currently in the field of cardiology, there are at least five pharmaceutical companies that are developing PCSK 9 inhibitors for lipid-lowering therapy[24,25]; as a result, there is an abundance of similar studies doing their rounds from each of these companies – including familial hypercholesterolaemia, mixed hyperlipidaemia, statin-resistant patients, and secondary prevention trials. Because of the uncertainty of clinical trials, many of the same units are taking on similar studies with various pharmaceutical companies and/or CROs. Careful planning is required to ensure that this does not result in selection bias being introduced into the study[26], especially with conditions that have greater prevalence in a particular population – such as familial hypercholesterolaemia in South Africa.

Regulatory Delays
Apart from a few countries, like Chile, who rely solely on ethics approval and a notification to the Minister of Health, most countries require the permission of the national regulatory (competent) authority[27]. Timelines can range from a few weeks up to 12 months, and can impact on study planning and conducting. The regulatory authority in South Africa has been particularly erratic in the last few years, with a number of clinical trials being lost or delayed as a result thereof[28]. Sites often spend many hours on pre-trial activities and then have very little or no time to recruit, thus preventing them from reaching their recruitment potentials. Fortunately, the situation in South Africa is showing strong signs of improvement in this regard.

Patient Recruitment
Patient recruitment is regarded as a leading bottleneck in drug development. This, together with delayed regulatory approvals, has put pressure on sites to begin looking for suitable patients prior to site initiation. However, the downside of this is that sites sometimes spend a lot of time and energy on a trial that does not even get initiated – especially seasonal trials like flu vaccine.

A number of issues plague trial recruitment:

- **Potential trial participant pool:** It has been estimated that only 4 % of US citizens participate in clinical research[23]. No corresponding figures for other countries are available. This low rate, together with the investigator's tendency to overestimate patient numbers during the feasibility stage, can have dismal consequences. Chang[30] identified the following reasons for patient non-participation in a chronic heart failure trial being conducted in Boston, USA – distance to site; time constraints; non-interest; health problems; transportation problems; and concern over experimentation. In a study of oncology patients, however, Meropol31 identified fear of side-effects as the greatest barrier to participation.

  In order to overcome this recruitment bottleneck, the potential participant pool needs to be expanded. A study conducted in May 2008 demonstrated that in the USA, 94 % of Americans have never been informed by their doctors of studies for which they might be eligible[21]. Understanding motivations for patient recruitment is an important step in increasing this pool. A previous study examined the motivation for clinical trial participation in a predominantly cardiovascular unit in South Africa, and demonstrated that altruism and learning about their condition were the leading reasons for participants to volunteer for clinical trials, even though benefits such as free access to medical care and medication also contributed[32].

- **Informed consent forms:** The increase in clinical trial litigation in both developed[33-35] and developing[36] countries has resulted in informed consent forms becoming increasingly long, complex and difficult to understand. Many are written at a high readability level and use technical language. A study performed by Terblanche[37] demonstrated that during the period 2000 to 2009, the mean ±standard deviation Flesch-Kincaid Grade Level for informed consents used in a South African unit was 12.13 ±1.8 (range, 8.3 to 14.9). The high readability scores utilised in this setting are not unique and are in keeping with the readability of these documents seen in other settings, including Australia[38] and the US[39,40]. However, the median level of education in the South African site was 6th grade, which is more than likely significantly lower than that observed in developed countries.

  The main concern with these increasingly complex informed consent forms is poor comprehension by potential trial participants. A number of studies have attempted to evaluate patients' understanding of informed consent issues in clinical trials, as summarised by Falagas[41], and many of these have confirmed this poor understanding

– especially in developing countries. In the latter case, language barriers have been cited as one of the contributing causes. In South Africa, for example, there are 11 official languages. This may give rise to the need for interpreters and the problems associated therewith – for example, the possibility that the interpretation is inaccurate and/or that the interpreters may omit essential information "in order to protect the patient from the harsh reality"[42].

An additional problem recognised with many of the black indigenous languages in Africa is the fact that formal writing is "a relatively new phenomenon", and "orthographics and vocabulary are still being standardised by piecing together spoken dialects"[43]. Pandiya[44] reports a similar problem in India where literal translations from English "do not capture the true meaning of concepts or phrases and the nuances of the original document changes on translation". The net impact of this is that readers often struggle to understand written language, even fluent speakers.

- **Patient advertising:** In an attempt to increase patient recruitment, many sites embark on advertising campaigns. Print advertising has been shown to be useful in South Africa with as many as 75 % of patients being recruited in this manner45. However, the effectiveness of this method is dependent on therapeutic area and patient population.

Internet advertising is emerging as an alternative to print advertising. The practice has been around for many years in developing countries, where it has been demonstrated that 20 % of clinical trials utilise the internet for recruitment46. From a South African perspective, the telecommunication infrastructure is not as advanced as that of first-world countries, but initial ventures into this form of advertising have been positive (unpublished data).

Technological Challenges

Technology has been used to support clinical trials for many years and the internet has become a fundamental part of the research process. The use of technology, as in all sectors, has increased the rate at which work is done[47]. However, attaining up-to-date, top-of-the-range technology, maintaining adequate connectivity and training staff to use the technology in the most efficient manner can be costly – especially in remote areas of South Africa. Technological challenges include:

- Although electronic data capturing (EDC) is intended to speed up the process, it is often hindered by the complexity of the protocol, poorly described eCRF guidelines, repetition and entering of redundant information which can easily be deduced by the computer software – for example age (when the date of birth has already been provided) and body mass index (when height and weight have been provided).
- Access portals such as iCloud for uploading of data are often not user-friendly, especially with regard to registration processes and periodic expiration of passwords. The Webcast training sessions on the portals are often very time-consuming and repetitive. Furthermore, once training is complete, sponsor companies require evidence of training and hence certificates and registration documents that need to be printed out at the site's cost.
- Laboratory reports, which were previously faxed to sites, are also increasingly becoming web-based. The burden then falls on sites to download and print the reports. Confusion occurs when some laboratories results are faxed whilst others are available online, resulting in duplicates being made or incomplete reports being received.

Monitoring Aspects

There has been a progressive transgression from traditional, 100 % source data verification (SDV) on-site monitoring. These days, more and more pharmaceutical sponsors and CROs are doing limited SDV – some companies reportedly as little as 16 %. In addition, the traditional on-site monitoring visits are being replaced by remote monitoring activities. The latest trend is "risk-based monitoring", where the extent and type of monitoring is dictated by findings at the site. A recent policy document by the Food and Drug Administration (FDA) showing support for this practice will no doubt result in further adoption of this practice[48]. This reduction in traditional monitoring, while hugely beneficial to pharmaceutical sponsors and CROs from both a financial and resource aspect, places a huge burden on the site. Quality control processes need to be implemented by sites, yet there is no additional budgetary allowance provided by the pharmaceutical sponsors or CROs.

The growth in the CRO industry has also resulted in frequent job-hopping amongst clinical research associates (CRAs). It is not uncommon to now have several CRAs during the course of a clinical trial. This frequent change in monitors further compromises the quality control process.

Patient Retention

As previously mentioned, the success of a trial relies heavily on patient recruitment and retention[28]. The loss of patients due to death, withdrawal of consent, adverse events and/or relocation may negatively affect the data validity and statistical analysis of the study[49]. Maintaining site-patient communication is fundamental to improving retention rates. This can often be problematic in South Africa, where many trial participants rely on cellular phones – especially with the use of so-called "pre-paid phones".

Retention gifts have been suggested as a method of encouraging patients to complete the study. However, this raises serious ethical questions, especially in South Africa where disparate socio-economic conditions manifest in a vulnerable patient population[50]. Even the fact that for many patients, access to otherwise unaffordable medical care while on a clinical trial can potentially be regarded as exploitative[32]. Nevertheless, retention is a continuous process, and there is a fine line between encouraging and coercing patients.

Budgets

Clinicians deciding to conduct research for drug companies receive less compensation for the work than in the past. According to a report from the Tufts University, the median grant amount held steady at about $60,000 from 1998 to 2003, despite a simultaneous increase in the complexity of clinical trial protocols[20]. Overall, the report states, so-called per-procedure, per-patient compensation for physicians declined by 27 % from 1998 to 2003. The budgeting process is fraught with challenges, which are often magnified in countries such as South Africa, including unobtainable screen failure rates, failure to keep up with inflation, tendency to pay quarterly and failure to adequately reimburse all study-related procedures[51]. A recent challenge for South African sites deals with the manner in which sponsors reimburse sites for archiving. In South Africa, it is mandatory to archive all study-related documents for 15 years. The cost of such a process is rarely less than ZAR 7000

and may exceed ZAR 100,000 for large studies (unpublished data). However, most sponsors regard a grant of ZAR 3000 as being sufficient.

Export Permits

According to the National Health Act of South Africa (Act 61 of 2003), clinical researchers are required to obtain an export permit from the South African Ministry of Health before exporting any tissue, including blood[52]. Delays in the issuing of these permits have been problematic for sites and have resulted in blood specimens being sent out of the country illegally[53]. However, failure to send these bloods can jeopardise the safety of the patient (not to mention the results of the trial).

Conclusion

South Africa has been involved in international drug trials since the late 1970s, although, with globalisation, the industry in South Africa has grown exponentially over the last few decades. Worldwide, there are many challenges for clinical triallists, but these are magnified in countries such as South Africa. This is largely attributable to the high number of vulnerable patients in a country marred by a poor national health policy. South Africa, however, has attempted to deal with these unique issues by enforcing GCP. In fact, it is the only country in which GCP is not only a guideline but a legal requirement, and where informed consent is stipulated in the bill of rights of the national constitution[28].

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