Clinical Trials in Low and Middle Income Countries
A Reflection on the Issues

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Introduction

The emergence of global clinical research has provided many benefits to medicine and science. Most significantly, global clinical trials have helped to speed up the testing process of new drugs to fight diseases. In recent years, there is a paradigm shift towards more large-scale clinical trials being conducted in low and middle income countries (LMICs), especially in East Asia and sub-continental Africa. There are several reasons for this: firstly, it has become increasingly difficult to test drugs in developed countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make recruitment of patients difficult. Furthermore, these patients are usually highly-educated and hence, would prefer a proven treatment over an investigational agent with uncertain efficacy and risks. Next, the economics of conducting a clinical trial in low and middle income countries are substantially more manageable. In contrast, in a developed country, groundwork costs of a clinical trial can run to 40 percent of drug development.

However, such trials have brought to light various issues related to patient safety, ethical regulations, relevant disease targets and overall social economics. Using a literature review approach, this article
attempts to highlight such ongoing areas of interest in the context of research being pursued in LMICs.

**Literature Review**

The analysis of the available literature was done using a search in Pubmed for relevant articles published from 2006 to December 2011. Additional publications were identified from the reference lists of shortlisted articles and non-systemic (i.e. literature-based) review articles. Any other related literature was also cross-referenced with the selected articles. However, relevant topic updates, discussions and commentaries before 2006 were also included if they met the following criteria: clinical trials in low and/or middle income countries, and relevant trials conducted in developing countries. A separate literature review with focus on ethical, legal and social scientific journals is being conducted, and the findings will be reported on a later occasion.

**Results**

**Common LMICs**

Many of the chosen LMICs usually had similar socio-economic conditions: they had a ready group of patients, good infrastructure, less ‘difficult’ patients and lax ethical constraints. One common example was India, an attractive site for clinical trials by pharmaceutical companies as illustrated in the literature search. Reasons cited included its genetically diverse large population of people who have myriad diseases, ranging from tropical infections to degenerative disorders.

**Disease variables**

The more common: Ischaemic heart disease

A global multi-centered trial by Orlandi et al assessed the outcomes of patients with myocardial infarction found that higher morbidity occurred in poorer countries. This was likely due to the higher risk baseline characteristics and longer delays in acute treatment in such places. Such differences reflect the underlying health differences in patients from LMICs, as compared to those from developed countries.

**The lesser mentioned: Cancer**

In general, cancer trials were usually under-reported; not only were published cancer clinical trials largely positive, but the results for most of the registered trials were nowhere to be found. An issue that was raised in *The Oncologist* is the possible failure of the pharmaceutical industry to publish disappointing results; less than 6 percent of industry-sponsored studies have been published and 75 percent of those published studies had reached a positive conclusion. As a significant number of cancer-related clinical trials are conducted in LMICs, the impact of such ongoing results should be better mentioned, especially when they involve vulnerable patients in an already socio-economically disadvantaged position. Another worry is that successfully validated interventions may be eventually unaffordable or unavailable for people in LMICs.

**Ethical Issues**

**A constant grey area**

Widespread illiteracy makes it particularly easy to sidestep the standard methods of obtaining informed consent. Investigators frequently enroll patients in trials as if their participation was a necessary step in their care. Few developing countries have resources needed to enforce good guidelines for research to be conducted ethically. They usually have few established Institutional Review Boards (IRBs) to turn to.

The difficulty in obtaining proper informed consent was highlighted in one paper. In a lawsuit between the Nigerian government and Pfizer, the accusation was that the latter had neither parental consent nor federal approval for the use of an experimental antibiotic on Nigerian children. In another ethically contentious case, the grim reality of how inadequate consent for trial substances was commonplace in developing countries was also highlighted. Here, a trial paediatric vaccine by GlaxoSmithKline (GSK) was administered to children in the rural areas of three Argentinian provinces. However, an inspection by the National Administration of Drugs, Food and Medical Technology (ANMAT) gave reason to believe that the parents of the participants did not fully understand what they were signing and the witnesses were not impartial.

**Some Inferences**

Despite ongoing obstacles, it is however, still important to conduct clinical trials in LMICs. The randomization of large numbers of patients in trials with hard clinical endpoints...
confers greater power to detect clinically important differences among higher-risk patients related to larger number of events. In order to achieve such results, it becomes necessary to include a large number of countries. It is also important to recognise that there are disadvantaged populations within developed countries that would benefit from clinical trials conducted in developing countries as well.\textsuperscript{10,13}

Furthermore, important diseases in question are usually prevalent in LMICs where the epidemiology, health services, social determinants of health, compliance patterns, and co-morbidities have a bearing on the way in which the health products will ultimately be used to achieve desired outcomes\textsuperscript{1}. Hence, multinational trials that include LMICs will allow wider applicability of results to the global community rather than trials that simply focus on industrialized countries\textsuperscript{2,23}.

Conclusion

An ongoing tedious challenge for healthcare researchers, government bodies and pharmaceutical companies will be to develop holistic, ethically sound clinical trials in LMICs, without compromising their already disadvantaged patients. The need to overcome the negativity of past failures should ultimately remain as top priority for good medical research to flourish.

References


About the Author

Sharon Low graduated with an MBBS from Monash University (Australia) and is currently an Advanced Surgical Trainee (Neurosurgery) from the National Neuroscience Institute (Singapore). She is in the midst of her research PhD in primary brain tumours. Her personal interest is in neuro-oncology and other CNS-related neoplasms, and her research interests are centred around primary brain tumours, in particular gliomas.