Doing cancer trials in India: opportunities and pitfalls

India’s population currently is 1.03 billion and is growing at 1.7% per year, which means that the country is adding 18 million people every year. In spite of the huge growth in population, India has made tremendous progress from being a net food importer in the 1970s to a net food and technology exporter and a large manufacturing hub. Per capita income has doubled since 1992 and there is an unprecedented economic boom in certain parts of the country fuelled by economic reforms and liberalization. Life expectancy was 35 years at independence in 1947; today it is ~65 years.

Cancer incidence is generally much lower here than in the developed world, the average national age adjusted rate being ~120 compared with >300 per 100,000 per year in developed countries [1]. The causes of low cancer rates have been variously attributed to under-reporting, ethnic and racial factors, lifestyle, food habits, and shorter life expectancy. Because of the sheer size of the population it is a safe estimate that India adds ~1 million new cases of cancer every year. It is a large country, the population of which is extremely heterogeneous and of very mixed genetic lineage. Patients are often diagnosed in late stages and have bulky disease. Cancer incidence shows significant variations in various regions, but more importantly the incidence of various types and organs affected also varies very widely [1]. For example, in males stomach cancer is the most common in the south, whereas lung cancer is most common in the north. In females, cancer of the cervix is more common in the south, whereas breast cancer is more common in the north. Other common cancers are head and neck in males and gall bladder in females, both comparatively uncommon in the West.

Clinical cancer research has undergone progressive globalization over the past decade. In the year 2002 the percentage of submitted studies done exclusively in USA decreased from a high of 80% to a recent level of 24% [2]. Clinical research organizations, both multinational and Indian, have been set up and are doing brisk business. The various reasons for continuous shifting of clinical trials scene to India and other developing countries from the Western world have been: (i) increasingly difficult and time consuming regulations in many parts of the developed world; (ii) extremely high costs; and (iii) non-availability of willing subjects. Some people have called it outsourcing, similar to what is happening in information technology, software and the manufacturing sector. In India the vast number of very diverse and advanced cancer cases offers a unique opportunity for carrying out different trials in various parts of the country [3]. The largest single advantage to the multinationals has been the ability to carry out trials in a shorter period of time as a result of faster recruitment [4]. Fortunately, benefits to India have also been immense: for the first time Good Clinical Practice (GCP) norms have been established in many parts of the country, which were virtually unheard of here before 1995. Because of funding through clinical trials, infrastructure has improved in many public hospitals that are perennially under funded. This has resulted in setting up of trial offices in some large cancer centers, with state-of-the-art facilities. Standard operating procedures have been established and there have been improvements in laboratory facilities. As scores of clinical trials are taking place, hundreds of staff are being trained and recruited for carrying out GCP trials. Many trials have been conducted successfully. In one study called the ABC (Adjuvant Breast Cancer) lead by the Institute of Cancer Research in Sutton, UK, India recruited 722 out of 3854 patients (18%) worldwide over a period of 6 years. In another ongoing adjuvant study in breast cancer, the ATLAS trial, India is the leading recruiting country, having contributed ~3000 out of 14,000 (19%) patients worldwide over a period of 7 years. It is only as a result of trials conducted under the guidance of NCI in Bethesda, MD, USA that treatment of childhood acute lymphoblastic leukemia and non-Hodgkin’s lymphoma has been standardized in many parts of the country [5]. These were institution-sponsored trials and enabled the investigators to close the recruitment faster. If India had not taken part these trials would have taken 2–3 years more to recruit so many patients. Since 1995 there have been many phase III trials sponsored by multinational drug companies. Some trials have resulted in Food and Drug Administration approval, such as letrozole by Novartis and voriconazole by Pfizer.

There have been some cases of abuse and misconduct, the most notable being the trials conducted by Cancer Centre Trivandrum in 2000–2001, wherein two new compounds called M4N and G4N that were discovered in USA were tested in 26 patients without proper regulatory approval [6, 7]. In another instance, the new aromatase inhibitor letrozole was being tested by some Indian drug companies for sterility in female subjects without proper approval. Recently, even the All India Institute of Medical Sciences (AIIMS), the premier medical institute in the country, was accused of carrying out stem cell research without following proper procedures, although AIIMS later denied this [8]. Whenever the government became aware of such misconduct, strict and prompt action was taken [9]. None of these reports of misconduct involved any major multinational drug company. On balance, the benefits of participating in international studies have far outweighed some disadvantages like exploitation and ethical misconduct. Most multinationals like GlaxoSmithKline, Roche, etc., have traditionally shied away from clinical trials in India because of what they perceive as weak regulatory framework and lack of patent laws. Last year, although US companies spent a total of $33 billion on new drug...
research, the US and other Western companies combined spent only $30 million (~0.1%) in India, certainly not a flood or exploitation by any standards.

Fortunately, things are changing. A new patent law has been enacted recently that provides patent protection, and it is expected that more companies will be encouraged to enter India for clinical trials. Also, in early 2005 another law was enacted that now allows pharmaceutical companies to conduct trials of new drugs in India at the same time as trials of the same phase are being conducted in other countries [3, 10]. Unfortunately, progress has been slow with regard to the office of Drugs Controller General of India, the authority that controls and regulates new drug approvals. The office continues to be poorly and scantily staffed in three rooms in a block in the Ministry of Health in New Delhi, and cannot cope with the increasing load of regulations and control. Things are looking up on this front also: the Union Health Minister has recently announced the setting up of the office of Drugs Regulatory Authority of India.

Although opportunities have been present in India for decades, effective regulation is only now taking shape. The situation is changing so fast for the better that many companies and organizations will be forced to make a start to get a foothold. There is always the possibility that illiterate and not properly informed subjects/patients could be exploited; I think this is going to be the biggest risk, and organizations and companies will have to be vigilant against this and have strict internal audits and inspections. I believe they will have to negotiate with a great degree of skill between the opportunities and pitfalls, and select their centers and investigators carefully. If any misconduct occurs it will put back the progress made in regulatory framework by years.

The Oxford Group lead by Professor David Kerr is currently in the process of establishing a cancer network of six publicly funded regional cancer centers, namely in Delhi, Mumbai, Ahmedabad, Hyderabad, Bangalore and Trivandrum, to carry out cancer studies in India. The network has been named as INDOX (INDia–OXford). Intense deliberations and discussions are going on, including visits to all these centers to ascertain their abilities, strengths and weaknesses. Establishing this network will hopefully also accelerate the process of good regulation and governance. There are plans to impart GCP training regularly, to establish quality control procedures and help out with the development of laboratories, especially in pharmacodynamics and pharmacokinetics. All the centers are keen and are cooperating in this effort. An important aim will be to address the problems of cancer that are more common in India, like head and neck, gall bladder, and cervix. India has, after all, benefited so much from scientific advances in the West until now, it is high time that it contributed significantly towards clinical trials on a global scale and also, in the process, addressed it own peculiar problems of cancer [11].

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References