Oncology Clinical Trials in Emerging Regions – A Trend Analysis
Cancer represents considerable unmet medical need and has been leading cause of death in economically developed countries and stands second in developing countries. Every year more than 11 million people around the world are diagnosed with cancer. The WHO has projected an increase to 16 million people in the next 15 years. This global burden of disease continues to thrive mostly due to aging and growth of world population with increasing adoption of behavioral patterns mainly smoking, physical inactivity and adoption of westernized diets, in economically developing countries. Majority of cancer patients die within short span of diagnosis. About 7 million people die from the disease representing to 13% of all deaths; this is projected to rise to 10 million by 2020. According to GLOBOCAN 2008 estimation, there had been 12.7 million cancer cases and 7.6 million deaths from cancer in 2008 only; of which 56% of cases and 64% deaths have occurred in economically developing world. In 2007, lung, breast and colorectal cancers in that order registered highest number of new cancer cases. For males, most common forms of cancers were lung & bronchus (incidence population - 1,108,731) followed by prostate (incidence population - 782,647) and stomach (incidence population - 691,432). In females, breast followed by cervix uteri and colorectal cancers were common types with an annual incidence population of 1,301,867, 555,094, 536,662 respectively. Furthermore, highest number of deaths was recorded from lung, stomach and liver cancer in that order. In males, lung & bronchus followed by stomach and then liver cancers gave highest number of deaths, whereas in females it was breast, followed by lung and cervix uteri that showed with highest number of deaths.

There has been a steady rise in cancer therapeutics within past few years primarily due to launch of new & highly specific targeted anti cancer drugs. For development of oncology therapeutics, substantial investments and commercial considerations are given priority rather than public health concern as investment ratio is more from private (private equities and others) than public (government and charities) investment. According to estimate on an average Pharmaceutical companies spend between $6.5 billion and $8 billion per year on cancer research. The oncology channel is largely rich as more than 2000 molecules are under development with >80 molecules in late stage development, which is expected to hit the market by 2015 thus flooding many of the cancer indications. The oncology market is forecasted to grow at CAGR of 9% from 2008-2015 to record a sales value of around $90.8 billion from estimated $49.6 billion in 2008 from top seven geographies. [1]

Clinical research has become noteworthy component to address the growing needs of global cancer burden in improving the lives of patients with cancer worldwide. As clinical trial business has gone global drug makers are seeking cheaper avenues for their studies and looking for bigger pool for treatment naïve patients. In addition, these companies are paying a lot more attention on emerging markets whose healthcare authorities are just like US & Western Europe keen in seeing cutting edge science being conducted in their backyards. Although, Clinical trials are the key to build a high value cancer system, yet it remains unavailable to most cancer patients.

1.0 Barriers in Cancer Trials

Clinical trials offers access to latest in cancer therapy by providing patients with state of art quality care and private practitioners with an opportunity to learn latest therapies before it comes to market, yet it is surrounded by many potential barriers. Owing to increasing costs and smaller number of drugs that gains regulatory approval accomplishing success for development of cancer drug continues to be challenging. The regulatory barriers are big hurdle as there are varying standards for approving new agents which fluctuates on country to country as there is no standardized regulatory process (i.e. safety monitoring, oversight,
investigator training). Moreover, differing legal systems and health system infrastructures (i.e., universal healthcare, government subsidized healthcare, privately-funded healthcare), language and cultural mores present further hindrance to regulations. In addition, there are several challenges associated with and transporting of biospecimens between and across countries which also adds to additional burden in getting regulatory approval. Ethical challenge is another obstacle for progress of cancer trial with respect to clinical trial design, use of placebo, protocol related issues, selection of patients for trial (more stringent if it involves vulnerable subjects including children). Patient recruitment represents a major burden on cancer clinical trial and for successful conduct of clinical trial achieving this cap of subject enrollment is essential. Patient gap is further enhanced by patient related barriers as subjects may have mistrust of research, cost of participation in the trial, transportation availability to reach the site, lack of education about clinical trials, fear, commitment to time and family issues.

In Latin America, factors that influence Latinos into research include language barriers (speak language other than English), immigration status, low literacy, low socio economic status (SES), fear and mistrust, limited access to health care, limited knowledge of cancer and risk factors, and cultural values of family. Factors linked with low SES considerably provide to greater mistrust, cancer fatalism, high rates of refusal to participate in research, and a lower likelihood of completing the research even if subjects initially agree to participate. As Latinos have great respect to their physicians and healthcare providers, collaborating with care providers, getting their endorsement and recruiting from care settings can facilitate participation. [2]

In Asia, language has many dialects each of which is attributable to specific geographic region and official translation of all clinical research documents are required even documents that are submitted to regulatory authority. However, in India which has several variations in culture and language conversion of clinical documents becomes an important matter. Therefore patient centered materials needs to take in account even the cultural and linguistic factors so as to ensure effective and clear communication is done between the sponsor, investigator and patient. Also, family values play a critical role for participating in study.

In Europe, cancer clinical trials are driven by European Organization for Research and Treatment of Cancer (EORTC) and have always posed multiple challenges which have become intense and complex after enactment of EU Clinical Trial Directive (EU CTD). Several major obstacles have emerged mainly for academic researchers due to its legal nature and overall costs for conducting cancer trials have substantially risen. Also, the global cost of EORTC insurance coverage has multiplied 5-folds from 1996-2006 with an increase ranging from 22% to 128%. Fees paid to Competent Authorities (CA) &/or EC for submitting clinical trial application has also contributed to rising cost under the directive. For non commercial sponsors, submitting an initial ethics committee application national difference in fees levied was from €0 to €2500 and from €0 to €1,000 when submitting a substantial trial amendment. Similarly was the fees paid to CA from €0 to €4,000 for an initial application and from €0 to €1,500 for a substantial amendment with waivers for non-commercial sponsors. Furthermore, obtaining a ‘Single Opinion’ ethics committee procedure remains major challenge of the Directive due to the variety of national models currently in use. [3]
2.0 Emerging Regions

2.1 Latin America

In Americas cancer is second leading cause of deaths with estimated 2.5 million new cases and 1.2 million
deaths annually in 2008 as per Pan American Health Organization. In Latin America, most of the countries
are facing an epidemiological transition where the disease burden is drifting from infectious to chronic
conditions with an increase in cancer rates. More than 70% of cancers are actually diagnosed when it is
incurable. In less developed countries cervical cancer continues to be a major threat, whereas breast and
prostate cancer rates are escalating in industrialized countries, primarily due to dietary changes and improved
standards of living.

<table>
<thead>
<tr>
<th>Country</th>
<th>Leading cause of death after CVS*</th>
<th>(ASR(W))** rate per 100,000 in 2008</th>
<th>New Cases excluding non melanoma skin cancer</th>
<th>Prominent cancer in Males</th>
<th>Prominent cancer in Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>2nd</td>
<td>206.3</td>
<td>104,900</td>
<td>Lung, Prostate, and Colorectal cancers</td>
<td>Breast, Colorectal, and Lung cancers</td>
</tr>
<tr>
<td>Brazil</td>
<td>3rd</td>
<td>100.4</td>
<td>321,000</td>
<td>Lung, Prostate, and Stomach cancers.</td>
<td>Breast, Cervical, and Lung cancers</td>
</tr>
<tr>
<td>Mexico</td>
<td>2nd</td>
<td>128.4</td>
<td>127,600</td>
<td>Lung, Prostate, and Stomach cancers</td>
<td>Breast, Cervical, and Liver cancers</td>
</tr>
</tbody>
</table>

*CVS-Cardiovascular System  
**ASR (W)):-age-world-standardized incidence rate

Latin American clinical research market has boosted due to adoption of clinical research regulations and
ICH-GCP standards. The market today is valued for time and cost efficient, accessible to compliant patients
and competent and enthusiastic investigators. Patient enrollment time is considerably shorter in spite of
having longer timeline in regulatory activity as compared to US & Europe and this achieves greatest savings.
The overall enrollment time is shorter as there are fewer trials competing for the same patient, also there are
more patients per site and patients are fairly easy to enroll than in US or EU. Furthermore, the region is
ethnically diverse and immigration is also to large extent from throughout the world. The number of deaths
from infectious diseases in Latin America is declining and mortality rates for cancer, heart disease and
strokes are rising. English is widely spoken in clinical research community, but Spanish remains
predominant language and Portuguese is primarily spoken in Brazil. The quality of data collected is
comparable to that of US & EU, due to quality investigators and knowledgeable in ICH- GCP guidelines.
Patients have great respect for their physicians and most of the investigators are well trained in US/EU. The
investigator involvement in the trial is particularly greater and this contributes to excellent patient retention
rates. As per clinicaltrials.gov, the region offers high potential for trial, as in fig 1 & fig.3; Brazil has
recorded largest number of trials both in Phase II & III followed by Argentina, Mexico, Peru and Chile. Also, highest number of breast cancer studies and cancer trials (from 2006-2011) was recorded in Brazil (fig.2 &4). Drug companies are more looking at this region as a promise and many industry trials are sponsored (fig. 5).

However, in spite of several advantages there has been increasing competition for patients & investigators and there are limited numbers of sites in each city. Rigid regulatory requirements cause delays and regulations vary with country specific procedures and timeline may vary from 3 to 6 months. Brazil requires about 18-35 weeks for regulatory approval. Studies involving placebos is difficult for getting approvals. Establishing good relations with regulatory authorities can shorten clinical development and approval times.

Fig.1: Phase wise distribution of cancer trials in Latin American Countries

![Fig.1: Phase wise distribution of cancer trials in Latin American Countries](image1)  
Source: ClinicalTrials.gov

Fig. 2: Number of trials conducted for top cancers in Latin American countries both sexes combined

![Fig. 2: Number of trials conducted for top cancers in Latin American countries both sexes combined](image2)  
Source: ClinicalTrials.gov
Fig. 3: Percentage distribution of cancer trials in Latin American countries\textsuperscript{[11]}

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>11%</td>
</tr>
<tr>
<td>Brazil</td>
<td>34%</td>
</tr>
<tr>
<td>Mexico</td>
<td>22%</td>
</tr>
<tr>
<td>Peru</td>
<td>13%</td>
</tr>
<tr>
<td>Chile</td>
<td>20%</td>
</tr>
</tbody>
</table>

Source: ClinicalTrials.gov

Fig. 4: Number of cancer trials registered in five Latin American countries from 2006-2011\textsuperscript{[11]}

Source: ClinicalTrials.gov
2.2 Central & Eastern Europe

There is a significant difference in risk of different cancers and varies by geographic area. Also, there were wide variation in quality of cancer care observed especially when compared between old and new EU Members or between developed and developing countries. In Central & Eastern Europe, there is > 25% risk of dying from cancer before age 75 to that in Western Europe. This is chiefly due to access to quality and varied treatment. Eastern Europe is especially hit with cancer. As per statistics over a million people die due to cancer every year. In Poland, nearly 70,000 patients suffer from cancer and death rate is as high as 70%. In Poland top 5 cancers in men are lung, prostate, colorectal, bladder, stomach and for women it is breast, lung, colorectal, ovary, and corpus-uteri. In Czech Republic 16,000 people die every year, and the total of patients is around 24,000. In Russia, over 240,000 people suffer from any type of cancer, from which 170,000 deaths results and over 140,000 reported new cases every year. In Bulgaria most common cancers are lung, prostate, stomach and breast with the incidence rates; 2962, 1092, 1640 and 3053 respectively. Cancer incidence in Russia has increased by 8% over last 10 years. The absolute number of cancer patients too has risen by 20% (thus, amounting to more than 400,000 people). As per the cancer registry, the highest incidence for men is lung cancer whereas for a woman is breast cancer, this rising incidence is attributable to rapidly aging population.

Due to death toll in this region many Pharmaceutical companies investigate cancer and related life expectancy which largely promotes clinical research in the region. The advantage of performing oncological studies in Eastern Europe is because the amount of new cases is extremely large and typical centralization of patients in large specialized centers makes it very good for reaching vast number of patients in a short span of time. In Bulgaria too there are many specialized labs like the National Oncological Centre that caters to successful conduct of basic and clinical trials 24 hours a day with many qualified specialists completely familiar with ICH-GCP standards. Also, infrastructure of the centre allows for clinical trials of diverse range of oncological indications to be undertaken successfully and be approved by regular inspections and audits.
In Russia, in the last decade there is a growing cooperation between investigators and multinational Pharmaceutical Companies in conduction of Phase I-III clinical trials. \(^8\) As per clinicaltrials.gov, highest numbers of trials are recorded from Poland followed by Russian Federation both in total trials conducted (fig.6) and trials done from 2006-2011(fig.9) and these countries also contribute to large percentage of trials conducted as compared to other CEE countries (fig.8). Lung cancer showed up highest type of cancer in Poland, followed by Russian Federation and Romania (fig.7). Central and Eastern Europe attracts lot of companies for having their presence in the region and makes an attractive destination for their sponsorship (fig.10).

Central & Eastern Europe has a centralized healthcare system with developed referral network (large, highly specialized hospitals still have important roles to play in the areas of oncology, cardiology and rheumatology). There is a good selection of high quality investigational sites across many teaching hospitals, medical schools and universities. The availability of patients is huge mainly from undeveloped populations, mainly due to lower economic status and limited reimbursement. The quality of data is superior which is confirmed by many audits & inspections in this region. Also, there is a low cost per completed case report form as less number of days is needed to recruit one patient. In spite of several opportunities in the region CEE is facing significant regulatory and legal challenges in several countries due to the EU accession and harmonization of regulations with EMEA requirements. \(^9\)

**Fig. 6: Phase wise distribution of cancer trials in CEE Countries\(^{[11]}\)**

Source: ClinicalTrials.gov
Fig. 7: Number of trials conducted for top cancers in CEE countries both sexes combined [11]

Source: ClinicalTrials.gov

Fig. 8: Percentage distribution of cancer trials in CEE countries [11]

Source: ClinicalTrials.gov
Fig.9: Number of cancer trials registered in CEE countries from 2006-2011[11]

Source: ClinicalTrials.gov

Fig. 10: Trials sponsoring bodies in CEE countries[11]

Source: ClinicalTrials.gov
2.3 Asia

Demographic characteristics vary widely in different countries in Asia. Median ages in India, China and Japan are 25, 34, and 44 years respectively, yet they have exhibited inconsistent burden of cancer. About 3/4th of new cases in liver cancer in males and 2/3rd in females occur in Asian countries. Furthermore, >50% of world’s new stomach cancer cases and >70% of newly diagnosed esophageal cases occurs in Asian countries. China alone contributes >1/2 of newly diagnosed liver and esophageal cancer cases and stomach cancer cases (42%). In 7 Asian countries, age standardized incidence rate and even mortality rate is high for lung cancer in males and breast cancer for females. In Asia population living with cancer are 3.6 million (males) and 4.0 million (females) of which China alone has 1.6 million males and 1.5 million female cancer survivors. In most of the Asian countries Colorectal cancer for males and breast cancer for females are among most common type’s survivors for cancer. As per GLOBOCAN 2008 statistics in Asia, risk of getting cancer before age 75 was 18% for males and 14.1 % for females and risk of dying from cancer before age 75 was 13.2 % for males and 8.7% for females. Five most frequent cancers for both sexes were lung, stomach, liver, breast and Colorectal in that order (ranked as per total number of cases). The cancer incidence rates in both sexes for all cancer sites tend to be highest in northeastern and lowest in southern Asian countries. [10]

Asia offers clinical development teams unique benefits for conducting trials. Due to rising incidence of cancer in Asia, the demand for quality products for treating the disease has skyrocketed. Therefore, large multinational Pharma companies have introduced their products with great success and this demand is further growing (fig.13.). With 60% of global population, Asian region provides highest number of available patients with varied ethnic diversity and hosts number of Pharma & Biotech industries giving a base for drug development. Asia presents an interesting mix of western knowledge and Eastern practice which has resulted scientific and medical advances. Top reasons for conducting clinical trials in the region includes established commercial presence, fast development, and large patient access pool, low cost for run of the trial (up to 50%) as compared to US & EU. Highly motivated and trained English speaking investigators, acceptable medical practice which supports conduct of clinical trial as per protocol designed in western countries, maturing regulatory structures and broad adoption of ICH-GCP guidelines. As per clinical trials.gov, the numbers of clinical trials have largely increased over past few years and contribution by each country for oncology trial is differing (fig. 14). The largest number of trial is conducted by Korea for Phases I-III (fig. 12), followed by China, Japan, Taiwan, India, Singapore, Thailand. As smoking is one of the potential causes for cancer, this is evidenced by rise in lung cancer cases in Asian countries Korea, China, Taiwan, Japan, Singapore, India, Thailand, Philippines, Indonesia in that order. Breast cancer is recorded as prominent form of cancer in Asian females (fig.12). During 2006-2011, largest number of cancer trial was witnessed in Korea, and then followed by China, Japan, Taiwan (fig.14). Asia has become prospective for conduct of trial over last several years and this can be seen by many Industry sponsored trials which have been growing exponentially (fig. 15).

Although, Asia offers a huge potential market, there is several hurdles mainly regulatory system and each country in the region has its own set of rules for approving and use of cancer products. Also, the pharmaceutical industry is under great challenge. Research based drug companies are making considerable changes to counteract negative impacts resulting from patent expirations and generic competition, rising R & D costs, falling productivity, pricing pressures and hostile regulatory environments for ensuring future success. Many countries require clinical testing of a product to prove that they are not only of consistent quality but matches to country safety standards. Owing to many regulatory barriers and diversity of required
documentation that was hindering simultaneous submissions in SE Asia, ASEAN countries started regulatory harmonization initiative which has given some space for companies to apply for regulatory filing to several countries in south East Asia.

**Fig. 11: Phase wise distribution of cancer trials in Asian Countries**

Source: ClinicalTrials.gov

**Fig. 12: Number of trials conducted for top cancers in Asian countries both sexes combined**

Source: ClinicalTrials.gov
Fig. 13: Percentage distribution of cancer trials in Asian Countries\textsuperscript{(11)}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig13.png}
\caption{Percentage distribution of cancer trials in Asian Countries\textsuperscript{(11)}}
\end{figure}

Source: ClinicalTrials.gov

Fig. 14: Number of cancer trials registered in Asian countries from 2006-2011\textsuperscript{(11)}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig14.png}
\caption{Number of cancer trials registered in Asian countries from 2006-2011\textsuperscript{(11)}}
\end{figure}

Source: ClinicalTrials.gov
3.0 Conclusion

The future of oncology looks promising as there are many molecules in late stage development of which many of them are for targeted therapies. Majority of companies involved in research on cancer are producing new molecules with an objective of niche cancer segment. With rising prices of anticancer drugs and increasing incidence rates of many types of cancers, spending on these drugs has risen faster than spending in many other areas of healthcare.

The cost of conducting clinical trials is also increasing at a very rapid rate and as drug development companies are also under great pressure because of rising R&D costs, expiry of blockbuster drugs, delays in completion of trials, and several other cost factors. These Pharma & Biotech companies are turning to emerging markets in order to reduce development cost, timelines and improve overall R & D productivity. The emerging market presents bright prospects and can fulfill the growing demand of these companies thereby pumping their own economy.

Based on the analysis, it can be seen that there is a good number of oncology Phase III clinical trials are conducted in emerging regions. As late stage clinical trials are the most conducive to cost and patient recruitment advantages found in the emerging regions where large number of well trained clinical research professionals and treatment naïve patients are available. In Latin America, Breast cancer is leading form of cancer, where large number of trials is reported. Whereas in CEE and Asia, Lung and Breast cancers has been the leading forms of cancer and more number of studies are conducted. Brazil, Poland, Korea attracts large number of Industry sponsored studies in Latin America, CEE and Asian regions respectively.
Though, each country has their own set of regulations, language barriers, culture related issues, these can be tackled in a collective and timely manner through proper set of documentation, leveraging local expertise and effective harmonization practice.

References
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