Patient Recruitment & Retention in Oncology Studies in Asia: Challenges & Best Practices
1.0 Introduction

Clinical trials on cancer have brought huge advances in arena of cancer prevention, treatment and diagnosis. However, cancer clinical trials are long and complex and need a varied approach than other therapeutic area trials and see a very less percentage of patient enrollments in the trial. With the advent of globalization of the clinical research enterprise recruitment of patients in clinical trial today has become more difficult and complex. The clinical trial leaders are surrounded by an ever increasing challenge of planning and conducting trials across different geographies with varying ethical, scientific, and cultural requirements and therefore regulating patient recruitment function is required to support the global drive toward innovation in drug development cycle.

2.0 Asia Focus

The key reason for global expansion of trial is due to the fact that developed clinical trial market of US and Europe are facing delays in the trial due to patient recruitment problems. Hence sponsors of clinical trials have been digging in emerging markets in hope that new patient populations would provide a ray of hope for on-time clinical trial enrollment and for this reason every aspect of development is moving east and Asia being seen as potential market for satisfying a lacunae in patient pool and filling up the enrollment gap. While it is true that in some countries patient enrollment rates is comparatively higher but they are not sufficient enough to give world region a distinct edge over others. Percentage of studies that actually complete enrollment on time is variably low in world’s leading clinical trial markets with Europe (18%), Asia Pacific (17%), Latin America (15%) and US (7%). In Asia, patient recruitment however may not be top five reasons for delay in clinical trial there are several other reasons like investigator selection and availability of study drug occupying top spots. [1] For running sites in Asia, it is said to hold significant cost savings and access to fast growing healthcare market in the world and tapping this region means navigating regulatory and operational challenges coupled with language barriers. As each country in Asia has its own discrete cost structure, diverse population, and standards of medical practice, infrastructure, governmental policies and differences in culture, drug and device developers even with established trials in Asia expanding from one country to next face serious obstacles. Therefore, selecting an optimal Asian country to establish or expand a trial depends on goals and priorities of each trial sponsor with indication and type of treatment being developed. [1, 2]

3.0 Asia Advantage

Pharmaceutical companies are well aware of the fact that conducting clinical studies is far more cost effective than running same study in US or Europe. Running a trial sites in China, Thailand, Philippines, and Malaysia can save 60% of trial cost compared with having equivalent site in western countries. [2] Also, most countries in Asia are 30-40% cost efficient than their western counterparts, but in some cases investigator salaries and other trial costs in countries like South Korea and Japan can be also as high if not higher like that of western world. Asia offers a large
patient pool having more than 4 billion people so sponsor would like to consider drawing patients from highly populous countries like India, China, Indonesia, Japan, Philippines and Malaysia. The incidence of target disease also plays a role in trial site planning and the region relatively offers more patients for first-line and second-line cancer drug evaluation than the West, where patient stores have already been exhausted. Countries like India have diverse subject pools who are afflicted with diseases of both developing and developed world. For certain diseases like breast cancer, lung cancer standard of care is similar to that of western world. Therefore, clinical trial sponsors feel easier in establishing trial sites in any Asian country. But, medical practice standards for many indications differ from east to west and between different Asian countries. In these situations, sponsors can look forward to Singapore, Taiwan, Hong Kong and South Korea for mirroring to western standards. Countries like South Korea and Taiwan are easing their regulations and facilitating protocol review and increasing their participation in global trials for advancing their medical practice standards. Singapore, South Korea and Taiwan have adopted an FDA flavor in their practices therefore sponsors don’t feel much of culture shock in dealing with them.\cite{1, 2}

4.0 **Challenges Ahead**

For successful conduct of clinical trial achieving a cap of clinical trial research participant enrollment is essential. From initiation of study to closeout a definitive number is required rather than a having a small pool of patients which may not be sufficient for defining goal of conducted trial which may otherwise be futile. Having enough enrollments gives a base for projected retention ensuring evaluative patient data and this final evaluative data further relies on retention of both subjects and investigators. However, in a cancer clinical trial accrual rate is relatively low and smaller percentage of adult cancer patients actually enroll in a trial. This rate is even lower among older persons, racial and ethnic minorities, individuals of low socioeconomic status who are treated as underrepresented population and these groups on the contrary have higher cancer mortality rates than entire cohort. These low numbers compromise on clinical research value and elevate vital questions regarding access to quality care and social justice for all communities affected by cancer.

Cancer trials could be of either therapeutic or preventive types. In some studies conducted about 150 distinct barriers were identified of which therapeutic trial had 124 barriers, 26 barriers was for preventive type of trial and 32 accrual barriers common for both therapeutic and prevention trials. Furthermore, there were many obstacles noted at patient level, provider level, design of the study level and healthcare systems level. Figure 1 shows number of studies that reported various barriers, of which mistrust of research and medical system showed up more whereas family issues was seen as less perceived barrier.
**Fig. 1:** Number of studies reporting on patient barriers to clinical trial enrollment (n=45 studies)\(^{[3]}\)

<table>
<thead>
<tr>
<th>Barriers</th>
<th>No. of Studies</th>
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<tr>
<td>Research method</td>
<td>20</td>
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<tr>
<td>Perceived barriers to participation</td>
<td>15</td>
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<td>Cost of participating</td>
<td>10</td>
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<td>Demographics</td>
<td>10</td>
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<tr>
<td>Lack of education about CTs</td>
<td>8</td>
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<tr>
<td>Fear</td>
<td>4</td>
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<td>Commitment to time</td>
<td>4</td>
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<td>Family characteristics</td>
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*CT’s indicates clinical trials

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**Fig. 2:** Conceptual framework, Barriers to recruitment \(^{[3]}\)

- **Study Design**
  - **Interventions**
    - **Moderators/Socio-demographic factors**
      - Race/Ethnicity
      - Age
      - Gender
      - Geography
      - Language
      - Income
      - SES
    - **Opportunity barriers/Promoters**
      - Lack of knowledge about CTs
      - Lack of knowledge about cancer
      - Culturally relevant education about CTs
      - Lack of physician
    - **Acceptance/Refusal barriers/Promoters**
      - Trust in person/Investigator
      - Perceived fees & benefits
      - Fear
      - Family
      - Costs
      - Time
      - Transportation
      - Altitude
      - Religious/spiritual beliefs

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*SES indicates Socioeconomic status  * CT’s indicates clinical trials
**Awareness**: As age progresses, the occurrence of cancer increases, and this may also be aggravated due to environmental factors. A significant number of patients in cancer trials are unaware of any trials related to their condition and are not receiving good and adequate medical care due to which enrollment falls. There are numerous studies that show education about trials was mostly a barrier to awareness. Other reasons included lack of culturally appropriate information, knowledge of cancer and physician awareness. In cases where cancers are undetectable in earlier stages until they become malignant, some physicians may not be able to detect them until later stages. Also, physicians may not be aware of a trial taking place and may assume that if a trial is happening it would be inappropriate for their patients. In cancer clinical trials where patients are sometimes referred, lack of support staff to support these referred patients proves to be a structural barrier. [3]

**Study Participation**: In most of the studies reported showed a close link between specific sociodemographic characteristics such as age, socioeconomic status, and racial/ethnic minority status along with lack or inadequate health insurance policies and reduced participation in clinical trials. Some subjects who actually looked forward for their enrollment in cancer trials were taken aback due to protocol study design that included co-morbid conditions, exclusion based on age, and having no reference of any physician for the trial participation. The most frequently reported barrier was the attitude of a provider (such as communication of the provider about the study, method of presenting information about the trial, data collection cost burden of the provider) and eligibility criteria (like co-morbid conditions, functional status). Furthermore, subjects who were not married and suffering from rare cancer conditions were reluctant to come forward in fear that their identity would be disclosed during the study. In recruitment of adolescents, parental influence also affected participation in the study which was difficult to separate. [3]

**Study Enrollment**: In some cancer studies reported showed a relationship between some specific factors that influenced the decision of subjects to participate in the trial. The obstacles were perceived harms of participation, uncertain about allocation of treatment during a trial, nature of intervention, time involved during a trial, loss of income, and transportation to the clinical trial site. Amongst all, the most frequently reported barriers were mistrust in research and medical system, family considerations, and patient-provider relationship. Mistrust in health professionals came from bad experiences of their friends and other close relatives. Further, health professionals have been shown in having prejudice among ethnic minority groups in whom cancer seems to be more prevalent. Such attitudes of health professionals are unacceptable and result in lack of trust, particularly when informed consent takes place and this behavior of physicians often leads to refusal of a subject to enter a clinical trial. Logistic barriers such as working for long hours, being in a manual occupation or low paid jobs, having no transport to reach the trial site and not being able to take time off from work were seen as potential obstacles. In addition, going for extra visits, dealing with side effects of intervention used in cancer trials, cost associated with travelling long distances, long waiting hours and complicated medical procedures were perceived as major hindrances. In one study, it was seen that...
a male subject was having difficulty in travelling to trial site and paying for taxis was beyond his limit and also found chemotherapy trial especially difficult due to side effects of the treatment and which was only overcome by encouragement and mental support received from trial nurses. [3, 4]

*Language & Culture*: - Lack of culturally relevant education especially in naive target population tends to increase communication barriers between subject and information provider during clinical trials. In South Korea for example several types of cancer are prevalent in Korean patient population, stomach and lung cancers are found in men and stomach, breast and cervical cancers are found in women. Due to high incidence of cancer 29% of multinational companies conduct trials in oncology in South Korea. As natives of South Korea have adopted western lifestyle habits, prevalence is expected to increase further. The Korean language has many dialects each of which is attributable to specific geographic region; however Korean is understood my most people and official translation of all clinical research documents are required even documents that are submitted to regulatory authority. But, this is not applicable to countries like India which has several variations in culture and language. Patient centered materials should take in account even the culture of target population as cultural context is essential in order to ensure effective and clear communication is done between the sponsor, investigator and patient. So documents such as informed consent, investigators brochure and patient reported outcomes could be a potential recruitment barrier if documents are not well translated and not addressed at target population in the region. In Korea and other Asian countries an importance is given to family in decision making unlike, in western countries where involving in a trial solely lies with the patient. Also, as physicians are highly respected in Korean society enrolling patients without the consent of their physician may affect subject recruitment and moreover, even if patient is enrolled entire history of the patient is not revealed by a physician, which is especially true for terminally ill patients. Therefore, such critical issue can drastically affect patient’s enrollment if a study wants to enroll subjects from this region. In some cancer trials fluency in English can be a hindrance in South Asian countries as some non-English speaking patients would not be able to take part if trial involves chemotherapy due to complicated and demanding nature of the trial. Also, lacking of fluency in English could lead to discrimination among such participants and this is thought to be a link to mistrust in health professionals. [3, 5]

*Terminology Difficulties*: - In some studies which are complex and stressful, terminology poses a difficulty in south Asian people in addition to fluency in English language that has already added to uncertainty and confusion. In one cancer trial it was reported that an older female insisted of having her daughter (who was fluent in English) to accompany her to chemotherapy and surgery due to her anxieties about the nature of trial. [4]

*Decision Making*: - As a subject is in itself suffering from cancer which is seen in a society as a backstage, in these cases the pattern of decision making is not same in Asians as compared to their western counterparts. Family and emotional bonding plays a very critical role with regards to a
subject’s participation in the trial. In a study reported showed that participants consulted with their family members and clinical trial staff too. Decision to be involved in the trial is also governed by gender of trial recruiter especially for trials which are like gynecological and breast trials and some studies reported that women would disagree to participate if a physician is of opposite sex and also trial staff. [4]

Consent Issues: - As informed consent is a very important document for subject’s participation in clinical trials ethically. There are several obstacles to this where subjects may not fully understand the objective of the study and reasons for signing it. In some cases participants view as a formality and other may sign it because others are signing it just because of social pressure too. Other subjects view it as a form of protection from their health practitioners in case if something has gone wrong in the past. Also, the staff who are involved in providing information to the subjects may withheld something useful like risks involved; may not be converse in subjects native language or may skip explaining what is beneficial to subject participation in the trial. The decision to participate in cancer trial is influenced by trial burden which is perceived as a potential barrier to participation. All such issues seriously hamper recruitment of potential subjects and retention of those already enrolled. [4]

Physician Barriers: - Physician irrespective of their specialty is regarded as gatekeepers to clinical trials. But, they have few apprehensions which make recruitment of patients in cancer clinical trial difficult. Sometimes health care providers don’t adequately understand conduction and importance of a clinical trial. They believe that clinical trial is not as good as treatment to a subject is currently undergoing. Moreover, they are uncomfortable in admitting about the uncertainty which treatment is best in Phase III clinical trial. As any clinical trial involves extensive paperwork like lengthy protocol, making to understand informed consent to subjects, and other regulatory and essential documents, so these documentation also adds to burden and extra time needed to train staff so as they can effectively recruit study participants. As recruitment and adherence are closely linked since those who are recruited have to be followed till completion of study as the inception cohort. Therefore, this gives an impact on subject recruitment both in terms of cost and screening and overburdened staff. Many oncologists say that they haven’t come across such type of patient who may be eligible for cancer prevention trial and also side effects of preventive medicines in healthy people is perceived as a block for participation of patients in a trial. [6, 7]

Socio-Economic factors: - In addition to cultural factors, socioeconomic status do play a role in patient enrollment in many Asian countries where clinical research is dominant as there is a vast range of difference between healthcare systems and government regulations. Japan which has most established clinical trial market in Asia with well developed healthcare and regulatory system equivalent to western countries runs high on cost of research due to strict government healthcare regulations. Taiwan, Singapore, South Korea and Hongkong have well developed healthcare system
and regulatory standards, research in these countries has high quality and have reduced cost to that of west. India, China, Indonesia, Malaysia, Philippines and Thailand have healthcare systems that are not quite as highly developed as those of other wealthier Asian countries, but cost of research is reportedly 2/3 times lower than the west. In above South East Asian countries due to low economic status greater part of population don’t have adequate access to healthcare services and therefore participation in clinical trials is the only opportunity for many patients for getting up-to-date treatment and in some cases no treatment at all. Also, as poverty rates and patient literacy rates vary in different Asian regions makes informed consent process difficult. [8]

5.0 Best Practices

(a) For successful accrual of study participants, selection of country and site plays a critical role depending on the nature of the trial and indication to be evaluated in terms of sponsor and thereafter patient recruitment training specific to a given indication/patient audience. A country feasibility report in terms of Epidemiology/Prevalence provides a thorough understanding of disease process and survival rate in a specific location. This report gives an understanding to sponsor for locating its target patient population and continuing further aspects of the trial. Other secondary parameters like cultural adaptation/translation of study materials, ethics committee support and version control and appointing a dedicated study co-ordinator at that site then becomes necessary consideration for implementation of trial and having a successful recruitment and retention of subjects.

(b) As a health care provider:-

- It is essential to maximize patients trust and support to patients who don’t feel comfortable with their ongoing treatment and for this it is necessary to assess patient’s feelings and attitudes about his/her treatment.
- Talk about any past experiences or myths about the research the subject is having like any misconceptions, lengthy informed consent, etc.
- Learn about patient’s fears and concerns in participation as they might have untrue perceptions regarding control group, receiving a placebo, side effects of treatment or fear of being experimented during course of trial.
- Give comprehensive information about the trial by physician himself or by study staff involved through print materials or videos.
- Discuss any potential costs involved like transportation costs, cost of tests involved and other routine checkups that are covered by the grant.
- Suggest remedy or reassurance for any logistical barriers such as complicated and time consuming protocols, repeated trips to healthcare center, competing with work and family demands.
- Involve patient’s family in any discussions related to trial, doing this can take care of any religious or cultural barriers and would eventually help potential subjects in a decision making and will feel less burdened and any kind of negative attitudes will be brought out in open.
Make certain that entire study related material is available in local languages and is well understood by the patient.

Ensuring that study staff involved must be committed in improving patient participation including minority communities.

Checking whether staff is thoroughly educated in explaining all clinical trial details to patients and sensitive enough to understand any barriers, myths, beliefs and norms which patient is carrying with him before a trial.

Diversify the staff in practice which ensures that having bilingual or multilingual staff can improve credibility of study where translations of study documents are required.

Selecting appropriate clinical trials and not being too ambitious for starting any trial. Clinical studies that requires extensive follow-up and difficult may not be conducive for patients.

Improve and foster relationships with community leaders, as relationship with these leaders can introduce trial staff to several educational programs and local meetings that can be useful to address the advantages of the clinical study to patient’s families, friends and neighbors. In addition, these leaders can also give quotes for brochures, newsletters and inserts into church bulletins

Form partnerships with local organizations like churches, surrounding associations, libraries, any groups/centers for spreading message regarding any clinical trials happening by means of brochures and newsletters. Also, as far as possible involve community leaders in designing recruitment strategies and materials.

Educating target population including community leaders and spokespersons regarding cancer as cancer related knowledge is poor in most people. Impart knowledge in terms of prevention, early diagnosis and various treatment options available.

Spread knowledge about cancer and cancer related trials in schools, churches and clinics by means local radio, posters, internet, and banners that can eventually help to increase awareness and eradicate any kind of barriers and thereby strengthening physician patient relationship.

Hold educational sessions for community doctors, nurses, coordinators and other medical staff which can serve as referrals or may collaborate in design and implementation of clinical trials. These liaisons would encourage open communication between oncologists and primary care physicians in the community.

Express the benefit of clinical trials for improving accrual rate that can include identifying potential solutions to health problems of specific populations who are unusually at high risk and in some cases providing free medical tests, physician evaluation and medication. For prevention or early detection trials target groups should know that cancer risk can be decreased and improve their health.

Sharing the findings of clinical trials within the community so as to increase future of potential enrollment and likelihood that community would receive maximum benefit from the research completed. [9]
(c) Designing of recruitment and retention strategies and effective risk management strategies should be a part of any cancer related trials. Key elements include use of validated tools that can predict study start up times, calculate variations in patient recruitment based on local holidays and customs and identifying problems in recruiting such that proactive interventions can be activated in order to keep the ongoing trial back on track. In some cases eligibility criteria should be revised keeping in mind country specific guidelines and restrictions so that they are more in line with the country practice. Critical factors for success of any oncology trial include early development of detailed recruitment and contingency plans, ongoing analysis of study start up progress, creation of infrastructure for patient outreach and screening. Identify the first site ready for initiation at a country level and identifying sites for prioritization, use of mutually agreeable informed consent forms and contract templates with sponsor and establishing alternative language for study related documents for sending to participating sites, designing of programs that includes reimbursement of trial related costs such as chemotherapy and supportive care, ongoing and in-depth analysis of screening and enrollment by site and country. \[10\]

(d) Community outreach programs play a major role in overcoming language and cultural barriers existing in different ethnic groups and community. Improved participation have been observed among ethnic minorities by use of culturally appropriate information and transformation in native languages and use of distribution materials about prevalence of certain diseases, prevention programs and access to clinical trial information. However, it is important that translators are native and are expert in field of clinical research and having knowledge about the indication to be discussed. \[11\]

(e) Individuals with low interest in prevention clinical trial would express low interest in participation in prevention trial irrespective of treatment type, perceived societal benefit or safety associated with the trial. In such cases researchers who are developing cancer prevention strategies must develop a more tailored education about prevention trials. On the other hand those potential subjects having moderate to high interest may have specific information sources (e.g.: physician, media/internet) or treatment parameters (like preference for lower side effects) that could significantly influence rate of participation in spite of having strong interest in learning about prevention trials. \[7\]

(f) As language and cultural barriers are prevailing in Asian region and there is a predominance of family decision making for potential patient participating in clinical trial. It is essential to take care of these hindrances beforehand. It is seen that Asian oncologists who communicate with their patients in local languages have had a greater success rates in the study. Also, many Asian women with cancer who received care from non-Asian oncologists were found to have needed language and cultural support through interpreters or patient navigators. \[12\]
6.0 Conclusion

A large proportion of clinical trials is being drifted in emerging markets of Asia primarily due to timely subject recruitment and cost effectiveness in the region. Several Asian countries are streamlining their regulatory procedures and increasing transparency to meet the ever growing demands. The tools are being created for having standard operating procedure in place and to have recruitment considerations in study infrastructure. In depth analysis reveals that more extensive application of best recruitment practice is needed in the region. Country selection, disease prevalence, patient motivation, site selection and infrastructure, cost, feasibility have to be evaluated for achieving optimum recruitment. In addition, language and cultural obstacles, efficient language translations needs to be done as per country specified norms for all study related documents so that patient better and completely understands the study and thus diminishing varied attitudes that prevails across patient, physician and medical system on the whole. Minority participation in clinical trials has to be increased, without which prevention, early detection and treatment disparity in mortality from cancers can’t be addressed. Community outreach programs should be put into practice for increasing awareness of both subjects and physicians which can enhance accrual rate and making more treatment options available. Carefully planned design, implementation and follow-up by sound recruitment and enrollment approach contributes to effectiveness and success of a trial from start to close-out.

References

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