The Pacific Rim

The challenging landscape of conducting clinical trials in the Western hemisphere has prompted an exploration of other world regions, especially in Asia Pacific due to its vast patient population

Dr Tracy Goeken at Linical Accelovance Group

In the US and EU, approximately 35% of trial delays occur as a result of patient recruitment, and one-fifth of the trials in these countries do not enrol a sufficient number of subjects. Shown in Figure 1, to expedite the recruitment process and avoid drug approval delays, both the US and EU have increased their number of registered clinical trials in developed Asian countries such as Japan, South Korea, China, India, and Malaysia (1).

It is well known that the primary barriers to conducting clinical trials in the US and Western Europe involve challenges in participant recruitment and retention, resulting in longer lead times and high costs (2). Furthermore, contracting qualified and experienced investigators and key opinion leaders add to the already lengthy trial times (3).

A 2013 analysis found that almost 57% of trials fail due to low patient accrual rates, which could translate into huge financial losses (4). Adding to this recruitment problem, racial and ethnic minorities, women, and the elderly are often under-represented in enrolments. For example, a study found that only 25% of elderly cancer patients enrol in trials, although they account for 63% of new cancer cases (5).

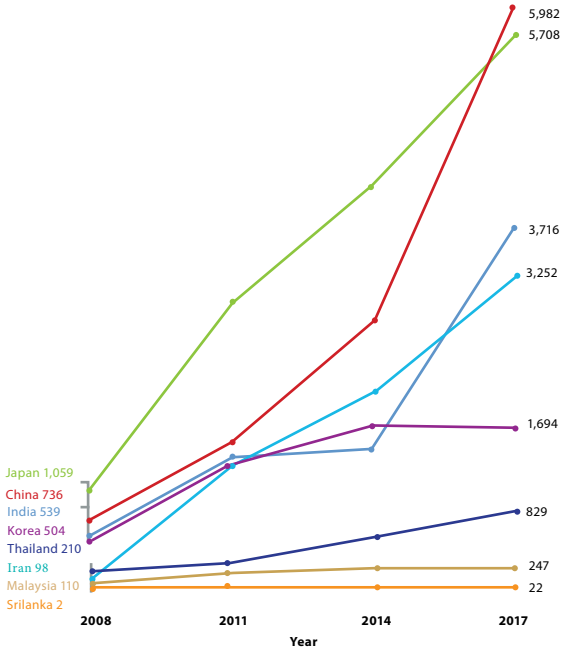

Figure 1: Annual changes in the number of all trials recruiting in Asia; data from WHO: International Clinical Trial Registry Platform (1)

These enrolment challenges in the US and EU have led to exploring other world regions such as the Asia-Pacific (APAC) rim, which is an attractive area to conduct clinical trials for numerous reasons (2,8):

- The presence of heterogeneous population groups and the availability of a large number of treatment naïve patients
- The high incidence of some diseases in Asian countries makes them the preferred recruitment site for treatment trials in cases such as liver cancer or gastroesophageal cancer – in South Korea or China, respectively
- Asia is also the most populated continent in the world, with more than half of the world's population, half of which located in urban areas
- The middle class in Asia will double over the next 10 years, with rising disposable incomes and health awareness making the region an important consumer market, warranting early engagement by sponsor companies at the clinical trial stage
- Clinical trial costs in Asia are about 30-40% lower than the US and EU, with the combined cost for each patient per visit in China, India, and Thailand nearly equivalent to the per patient per visit cost in the US alone
- Worldwide-accepted data quality: the percentage of EMA critical findings and US FDA official actions taken during inspections are lower in Asia than North America, reflecting a high quality of international compliance

- A growing network of US-managed hospital affiliations in the APAC region (e.g., Cleveland Clinic and Mayo Clinic) that strengthens opportunities for sponsor companies to conduct clinical trials
- Per capita government spending on healthcare in Asian countries is lower than in the US and Western Europe, providing an opportunity for clinical trials to be an effective way for Asian patients to gain access to innovative therapies

Shown in Figure 2, a 2016 analysis demonstrated that the number of clinical trials conducted in Asia per capita is less than 5%, compared with 166% in the US, 123% in Germany, and 64% in the UK (2).

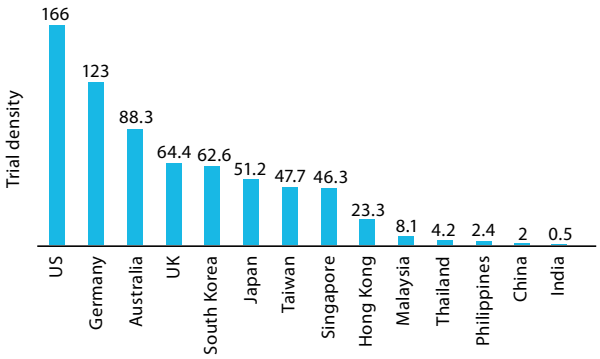

Figure 2: Clinical trial density in selected countries, 2016 (2). Note: trial density is the number of recruiting sites for industry-initiated trials on 14 April 2016, divided by the country population in millions

As one of the largest pharmaceutical markets in the world, APAC's share is growing at a faster pace than the US and Europe. APAC's pharma market is forecasted to grow at a 7.7% compound annual growth rate from 2015 to 2020, compared with 4.6% for the US and 2.7% for the EU in the same time period (8). By 2020, APAC will account for more than 30% of pharmaceutical sales growth worldwide, making it a critical revenue source for biopharma companies (9).

Disease incidences in the APAC region that are similar to, or higher than, that of Western countries are creating recruitment opportunities in large patient pools (8,10). The high incidence rate of stroke, hepatitis, and lung cancer make APAC an attractive destination to conduct clinical trials, and clinical trial penetration in the APAC region is low when compared with the US, which could simplify recruiting. Limited government or insurance reimbursements make clinical trials a way for patients to gain access to novel therapies that they otherwise could not avail (8).

Recruitment is often a challenge in conducting trials in the West because of a smaller patient pool and a higher number of trials. Furthermore, practising clinicians often do not refer patients to clinical trials (11). This impacts enrolment and sometimes results in the termination of trials. The penetration of trials in APAC is also less (see Figure 2), offering a more treatment-naïve population. A lower density of clinical trials in the APAC region (less than 5% in China, Thailand, Philippines, and India) provides an additional advantage in patient recruitment from a pool of approximately 4 billion people, of which more than 2 billion live in easily accessible urban areas (12).

Another significant driver is the availability of strong therapeutic area expertise and specialised disease centres. In South Korea, Wooridul Spine Hospital is one of the top global spinal treatment hubs, with more than 1,130 neurospinal specialists and state-of-the-art technology (13). Singapore's Gleneagles Hospital is the leading centre for cardiac care, and its Asian Center for Liver Diseases and Transplantation is the first private facility for liver diseases, with a worldwide consensus honour from the Joint Commission International for quality patient care (8). The world's biggest hospital is Zhengzhou Hospital in China, which has 7,000 beds and performs 196,000 operations annually, and there are plans to increase the number to 10,000 beds over the next couple of years (14); the second largest hospital in the country, West China Hospital in Chengdu (in Sichuan province), by comparison, has just 4,300 beds.

Sir Run Run Shaw Hospital, a Hangzhou-based healthcare system, has joined the Mayo Clinic Care Network, a group of independent organisations committed to improving the

"Another significant driver is the availability of strong therapeutic area expertise and specialised disease centres"

> **The APAC region appears to be an ideal recruitment opportunity for conducting cost-effective clinical trials**

quality and delivery of healthcare through collaboration (15). Sir Run Run Shaw Hospital, which is affiliated with the Zhejiang University School of Medicine, is the first healthcare system from China to join the network. The formal agreement with Mayo Clinic promotes a close clinical relationship that focuses on sharing medical expertise and knowledge to benefit patients. The Cleveland Clinic is making a name for itself in China as well with a new partnership in Shanghai. Through a new international affiliation programme, Cleveland Clinic Connected (the local health system) announced that it will team up with Luye Medical Group to provide Cleveland Clinic's best healthcare practices to the Shanghai New Hongqiao International Medical Center (16).

Little is known about factors influencing trial recruitment in Asian patients. A recent study of multi-ethnic Asian women with breast cancer found that facilitators and barriers to trial participation were similar to those previously reported in Western women (17). Unique sociocultural factors suggest that approaches that are customised to local and community beliefs are needed to improve trial participation in minority groups. For example, patient autonomy is often the guiding principle in decision making, and trial recruitment often involves consent from the patient only. However, in some Asian cultures where decision making involves the community and family, influencing attitudes and opinions in the larger community may be an important first step before patient recruitment. Both Chinese and Malay women expressed a lack of knowledge about the purpose and processes of clinical trials and showed inadequacy in making decisions. Patient education may need to be more intense and address literacy as well as cultural barriers to improve recruitment. Trust in their own (but not in other unknown) physicians was a dominant theme among participants, which suggests that recruitment may be more successful if conducted through the patients' own primary care physicians and oncologists.

Lymphoma is among the leading causes of cancer-related deaths in China. It was reported that about 88,200 people were diagnosed with lymphoma in China and about 52,100 people died from the disease in 2015 (18). For lymphoma patients who fail to receive standard treatment, enrolment in a clinical trial is the first recommendation. However, patient recruitment to clinical trials is a big challenge in China. Limited available data on recruitment rates of lymphoma patients in China has suggested less than 10% of all cancer patients actually participate in clinical trials throughout the course of their treatment (19).

A 2017 study of 177 lymphoma patients by Kong Q *et al* stated the top five reasons facilitating a decision to participate in clinical trials (20). These included a thirst for new treatments (100%), trust in the hospital (96.6%), trust in doctors and their advice (96%), the idea that clinical trials may be more effective than conventional therapy (76.3%), and expectation/hope of better treatment by doctors/staff (72.3%). The top five barriers to trial participation included a lack of knowledge about clinical trials and not wanting to try (94.2%), concern about the side effects and safety (93.5%), worry about the effectiveness of a new drug (81.8%), the idea that the relevant laws and regulations were imperfect and the rights of patients could not be guaranteed (76.6%), and the idea that clinical trials were not necessary (60.4%).

Unlike the US and EU, the APAC region appears to be an ideal recruitment opportunity for conducting cost-effective clinical trials that can utilise a pool of treatment naïve subjects in a populace approaching 4.5 billion. The emerging clinical trial markets, particularly China, South Korea, and Taiwan, offer genetic diversity with a potential to provide higher quality and generalisability in clinical trial data. However, several challenges also exist for Western sponsors in the majority of the Asian countries where regulatory, operational, and infrastructural challenges are at the forefront. Recruitment barriers are many, but can essentially be grouped into physician-related, patient-related, and system-related factors. The consensus opinion appears to suggest that sponsors and clinical researchers need to pay more attention to both individual factors in terms of educating the patient and physician, as well as community cultural factors when considering recruitment strategies. In this regard, working with regional partners in APAC countries could prove a very valuable asset to Western sponsors who wish to overcome some of these recruitment barriers.

References

1. Ali S *et al*, Clinical trials in Asia: A World Health Organization database study, *Perspect Clin Res* 10(3): pp121-3, 2019
2. Visit: novotech-cro.com/sites/default/files/170217_FrostSullivan_Asia%20white%20paper_full.pdf
3. Visit: www.ncbi.nlm.nih.gov/books/NBK50892
4. Williams RJ *et al*, Terminated trials in the ClinicalTrials.gov results database: Evaluation of availability of primary outcome data and reasons for termination, *PLoS One* 10(5): 2015

5. Unger JM *et al*, Impact of the year 2000 Medicare policy change on older patient enrollment to cancer clinical trials, *J Clin Oncol*: 24(1): pp141-4, 2006
6. Visit: www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics
7. Visit: ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm
8. Visit: www.cmicgroup.com/files/user/en/solution/pdf/Whitepaper_201710.pdf
9. Visit: www.bcg.com/publications/2016/pharma-playbook-success-southeast-asia.aspx
10. Visit: www.worldlifeexpectancy.com/world-health-review/united-states-vs-china
11. Visit: www.ncbi.nlm.nih.gov/books/NBK220370
12. Visit: www.worldometers.info/world-population/asia-population
13. Visit: wooridul.com
14. Visit: www.weekinchina.com/2015/07/the-world%E2%80%99s-biggest-hospital
15. Visit: newsnetwork.mayoclinic.org/discussion/sir-run-run-shaw-hospital-in-china-joins-mayo-clinic-care-network
16. Visit: www.cleveland.com/healthfit/2018/07/cleveland_clinic_expands_to_ch.html
17. Lee GE *et al*, Barriers and facilitators for clinical trial participation among diverse Asian patients with breast cancer: A qualitative study, *BMC Womens Health* 16(43): 2016
18. Chen W *et al*, Cancer statistics in China, 2015, *CA Cancer J Clin* 66(2): pp115-32, 2016
19. Li JY *et al*, Participation in cancer clinical trials as viewed by Chinese patients and their families, *Oncology* 79(5-6): pp343-8, 2011
20. Kong Q *et al*, Barriers and facilitators to participation in clinical trial among lymphoma patients from Sun Yat-sen University Cancer Center in China: An observation study, *Medicine (Baltimore)* 96(37): 2017

About the author

As Chief Medical Officer of Linical Accelovance Group, **Dr Tracy Goeken** is responsible for providing strategic and operational leadership regarding the company's global medical and scientific operations. Dr Goeken oversees clinical development functions and activities within the company, including medical, regulatory, medical writing, and pre- and post-market pharmacovigilance departments ensuring global alignment and operational excellence. Tracy received his MD from St. Christopher's College of Medicine, UK, having completed his clinical training at LSU Health Sciences Center in Louisiana.

Email: tgoeken@linical.accelovance.com