



ASIA: PREFERRED DESTINATION FOR CLINICAL TRIALS

A Frost & Sullivan White Paper



Table of Contents

Executive Summary	3
Introduction	4
Key Challenges Of Conducting Clinical Trials In The United States And Western Europe	7
Why Asia Is A Preferred Destination For Clinical Trials	9
Key Challenges Of Clinical Trials In Asia	27
Critical Factors In Selecting A CRO For Clinical Trials In Asia	32
Last Word	35

Executive Summary

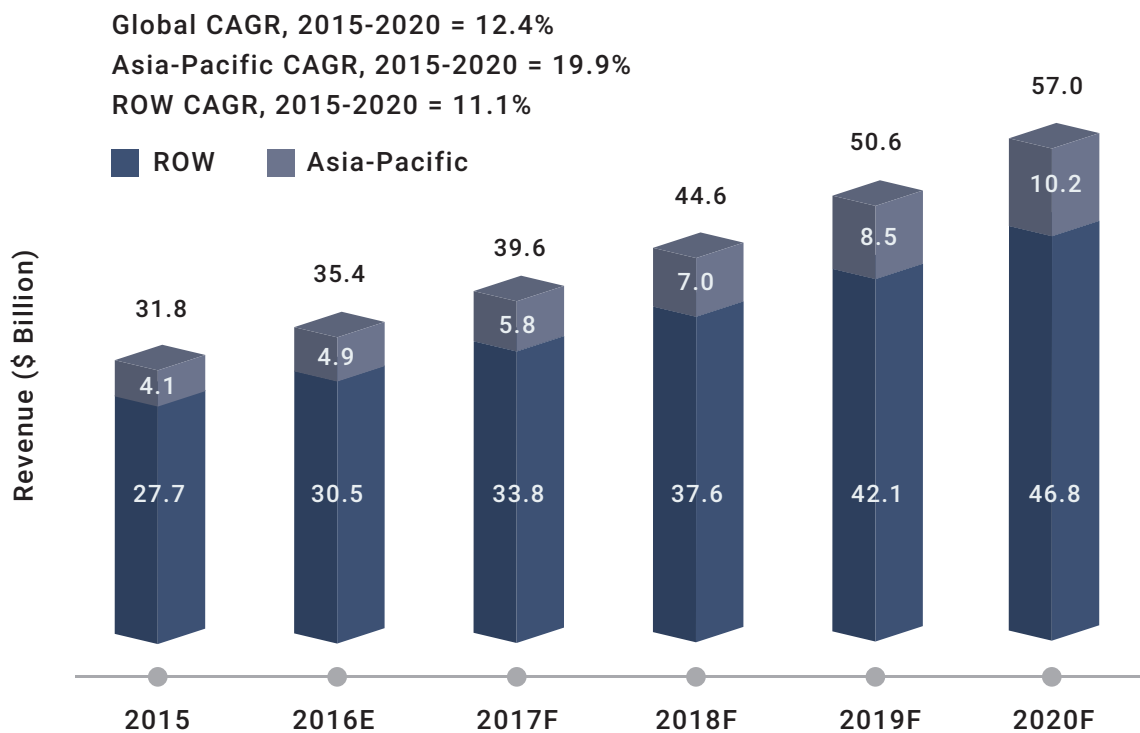
WHAT	<p>The clinical trials process is complicated and time-consuming, requiring substantial investment. Biotechnology and pharmaceutical companies in the United States (US) and Europe face escalating clinical trial costs and challenges in both recruiting and retaining patients. Additionally, companies have to navigate through complex regulatory processes.</p> <p>To overcome, these challenges, US and European biotechnology and pharmaceutical companies outsource their clinical studies to contract research organizations (CROs).</p> <p>This white paper highlights research on why Asia is a key destination for clinical trials.</p>
WHY	<p>Availability of vast patient pools, high-quality infrastructure, comparable quality and lower costs appeal to US and European companies.</p> <p>There are 3 key benefits in outsourcing clinical trials to Asia:</p> <ul style="list-style-type: none">• Resources, Capabilities and Speed: Elements unique to Asia include large treatment-naïve patient pools, numerous clinical trial centres with advanced equipment and technology, comparable incidence and prevalence of Western diseases. The region's knowledgeable physicians and Key Opinion Leaders (KOLs) provide attractive environments for clinical trials and facilitate speedy trials; while low healthcare spend by many governments in Asia makes clinical trials an attractive way for patients to access innovative therapies in these countries.• Worldwide Data Acceptability: Data from clinical trials in Asia is routinely accepted as part of US Food and Drug Administration (US FDA) and European Medicines Agency (EMA) regulatory submissions. KOLs from Asia are often members of international expert groups and citable academic output from Asia is growing rapidly. Data from inspections conducted in Asia by US FDA and EMA show low levels of adverse findings versus the US or European Union (EU), indicating high international compliance to standards.• Cost-Effectiveness: Costs in Asia for procedures, diagnostic tests and visits are generally 30-40% lower than the US and European countries.
WHO	<p>Key factors to consider when selecting a CRO:</p> <ul style="list-style-type: none">• Capability: The CRO should have a capable in-house team with strong project management skills and a keen understanding of regulatory requirements. A client-centric and flexible approach to project delivery is another attribute to look for. The CRO should also offer scalability of IT systems and sophisticated quality systems.• Experience: Expertise in specific therapeutic areas, study types and trial phases; proven track record of trials in the biotech sector and with multi-region trials; and a thorough understanding of regulatory audits.• Network: CROs should have a local presence and networks, and strong relationships with the principal investigators, KOLs, and institutions. CROs should also be flexible in their approach to working with multiple regional specialist CROs.

**Note: The currency used in the document is USD.*

Introduction

Outsourcing is an integral part of the biopharmaceutical industry's value chain, primarily during the clinical phases of research and development (R&D). The increasing cost of research, the loss of revenue from leading blockbusters going off patent and the lack of extensive in-house R&D infrastructure has driven many biotechnology companies to outsource clinical trials to contract research organizations (CROs).

Figure 1: Total CRO Market Forecast, Asia-Pacific and Rest of World (ROW), 2015-2020F



Note: F: Forecasted;

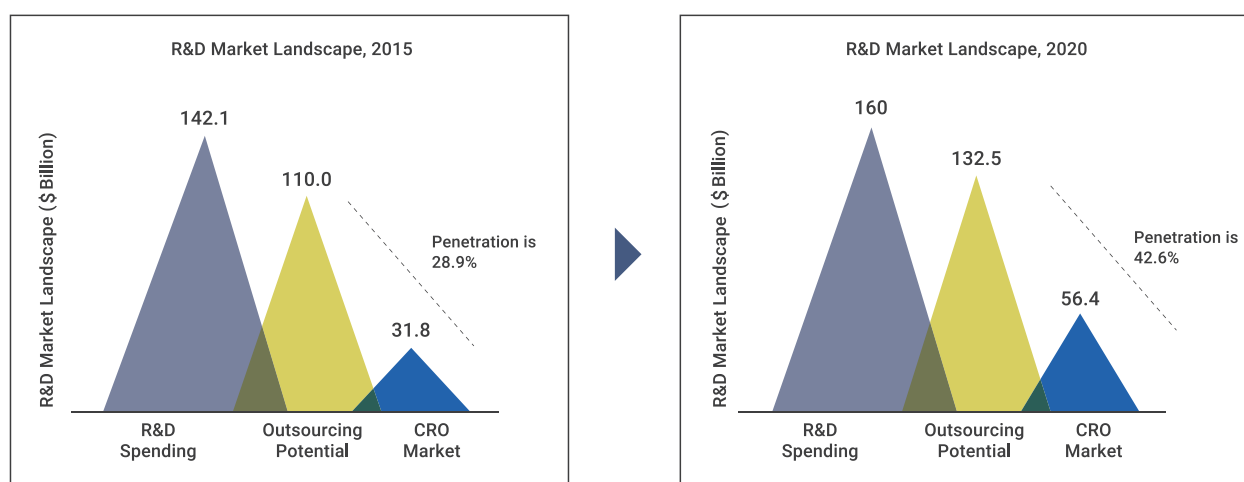
Source: Frost & Sullivan Global CRO Report, 2015; Frost & Sullivan APAC CRO Market Report, 2015

The clinical trial market has continued to show robust growth.

As shown in Figure 1, globally clinical trials are expected to grow at a compound annual growth rate (CAGR) of 12.4% to reach \$57.0 billion in revenue in 2020 from \$31.8 billion in 2015. During 2015-2020, while the CRO market in North America is expected to grow at 10.4% CAGR, the Asia Pacific CRO market is forecasted to grow at a CAGR of 19.9%¹. The key drivers for this growth are increased R&D activity and shift toward outsourcing.

More than three-quarters of R&D spending by biotechnology and pharmaceutical companies can be potentially outsourced. We can expect to see a significant increase in the CRO market, through increased outsourcing alone with penetration expected to increase from 29% in 2015 to 43% in 2020² as shown in Figure 2. Asian growth is expected to be even higher as clinical trial penetration in Asia in 2015 was even lower than the global penetration, at around 15%.

Figure 2: Total CRO Market, R&D and Clinical Research Outsourcing Landscape, Global 2015-2020F



Note: F: Forecasted;

Source: Frost & Sullivan Global CRO Report, 2016

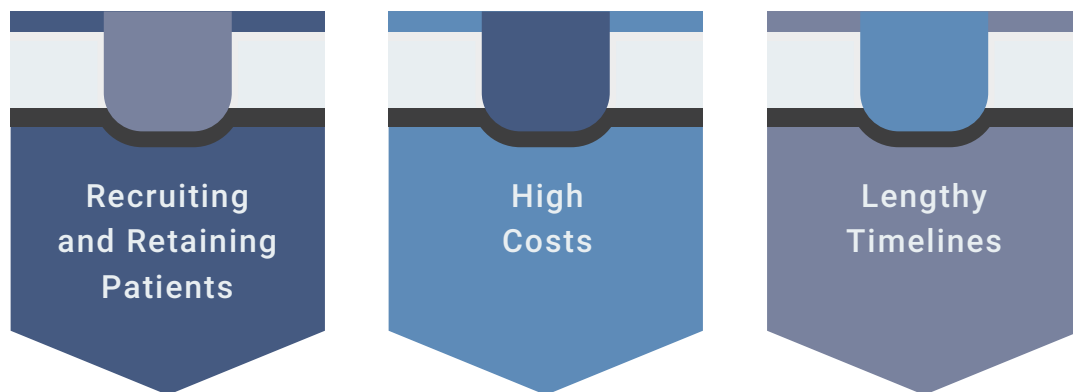
Asia is well positioned to become a preferred destination for clinical trials, due to a number of attractive traits.

- **Availability of treatment-naïve patients for speedy recruitment:** A pool of approximately 4.0 billion people, with more than 2.0 billion in easily accessible urban areas.
- **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 high quality of international compliance.
- **Attractiveness of trials to patients:** Per capita government spending on healthcare in Asian countries is lower than in the US and Western Europe. This creates opportunity for clinical trials to be an effective way for Asian patients to get access to innovative therapies.
- **Western disease patterns:** Asian countries show similar disease patterns for major diseases to Western nations, providing a comparable environment to conduct clinical trials. Some pockets of high incidence may provide advantages in certain therapeutic areas.

- **High quality infrastructure:** Numerous specialized clinical trial centers boast state-of-the-art equipment and advanced technology. Fast-growing Asian economies are leapfrogging the traditional path of enhancing legacy information technology (IT) systems and are at the forefront of innovation.
- **Cost:** Asia offers lower costs for clinical trials. For example, costs in China and India are 25% to 40% lower than that of Western countries³.

This white paper, based on Frost & Sullivan primary and secondary research, explores the key factors that position Asia as a destination of choice for biopharma companies to conduct clinical trials. The report highlights case studies of international biopharma companies that have conducted clinical trials in Asia using CROs. It also examines the important criteria that biopharmaceutical companies must consider when selecting a CRO.

Key Challenges of Conducting Clinical Trials in The United States and Western Europe



Broadly, 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. Finding qualified and experienced investigators and key opinion leaders (KOLs) add to the already lengthy trial times⁴.

Recruiting and Retaining Patients

Failure to meet patient numbers or timelines can delay product launch. A 2013 analysis found that almost 57% of trials fail due to low patient accrual rates that could translate into huge financial losses⁵. Racial and ethnic minorities, women, and the elderly often are underrepresented in enrollments. For example, a study found that only 25% of elderly cancer patients enroll in trials, although they account for 63% of new cancer cases⁶.

Low participation has encouraged more biopharmaceutical companies to pursue clinical trials beyond the US and Western Europe. A study of 24 cardiac trials in the US found that 19 trials, with a total of more than 151,000 patients, included international participation⁷. One trial for HIV-associated cryptococcal meningitis recognized low US patient enrollment and subsequently added Thailand as a trial site, where it recruited 99 patients in 5 sites. The trial added an average of 4 patients per site in Thailand over 3 months compared with 1 per site in the United States⁸.

The majority of Western European trials now look at international destinations for patients. According to EMA clinical trial data submitted between January 2005 and December 2011, 62% of patients were recruited from outside the European Economic Area and Switzerland⁹.

High Costs

A 2014 study estimated the cost of developing a prescription drug and gaining market approval at \$2.6 billion¹⁰. The time and costs associated with conducting trials in the European Union have grown significantly due to higher insurance fees and increased administrative and resource cost for the trials¹¹. High costs are increasing the scrutiny companies and research centers give to the type of projects they take on, in terms of profitability¹². For instance, the willingness to undertake drug studies for orphan conditions, acute disorders, and diseases prevalent in poor countries is low compared with those that offer high sales potential. Many biopharma companies are exploring ways to reduce drug costs, including undertaking clinical trials in lower cost locations.

Lengthy Timelines

The clinical trials process can be time-consuming. The average time from clinical testing to gaining approval to market the drug is roughly 7 to 8 years, while the full process from discovery to registration takes between 11 and 15 years. The lengthy review times of both the US FDA and the EMA add to the drug development process. Though both organizations have introduced priority procedures to minimize delays in launching clinical trials, the drug development process as a whole remains lengthy^{13,14}.

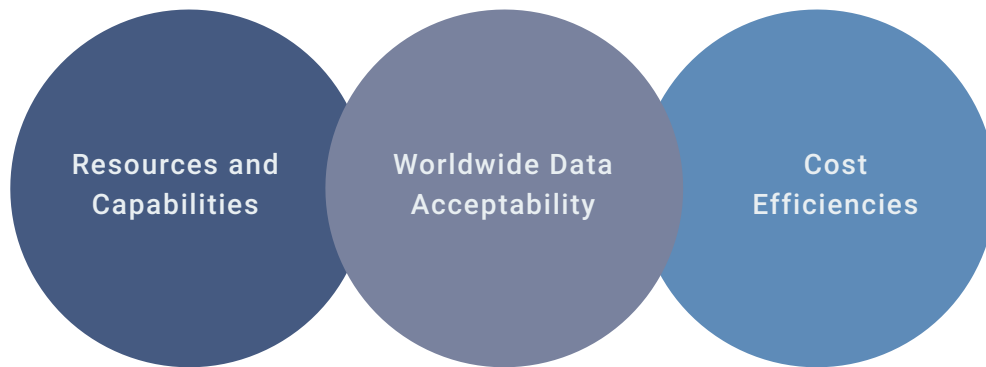
Navigating complex regulatory and administrative tasks are also issues. For instance, regulations concerning informed consent and patient privacy enacted through the US Health Insurance Portability and Accountability Act (HIPAA) and unclear regulatory pathways for certain disorders affect the duration of clinical trials. In the US, sponsors must not only follow federal regulations but also adhere to state and local policies in multi-site trials. The same challenges apply to European Union member country policies.

Developed nations, while bringing a lot of clinical research expertise, also bring significant clinical trial competition. The costs tend to be higher; and as part of cost conservation efforts, we must execute clinical trials in countries that can work within our existing infrastructure, such as an ability to export tissue samples to our US central lab for eligibility determination. The Asia-Pacific region is an attractive area for these reasons.

Associate Director, Clinical Trial Management, US Biotechnology Company



Why Asia Is A Preferred Destination For Clinical Trials



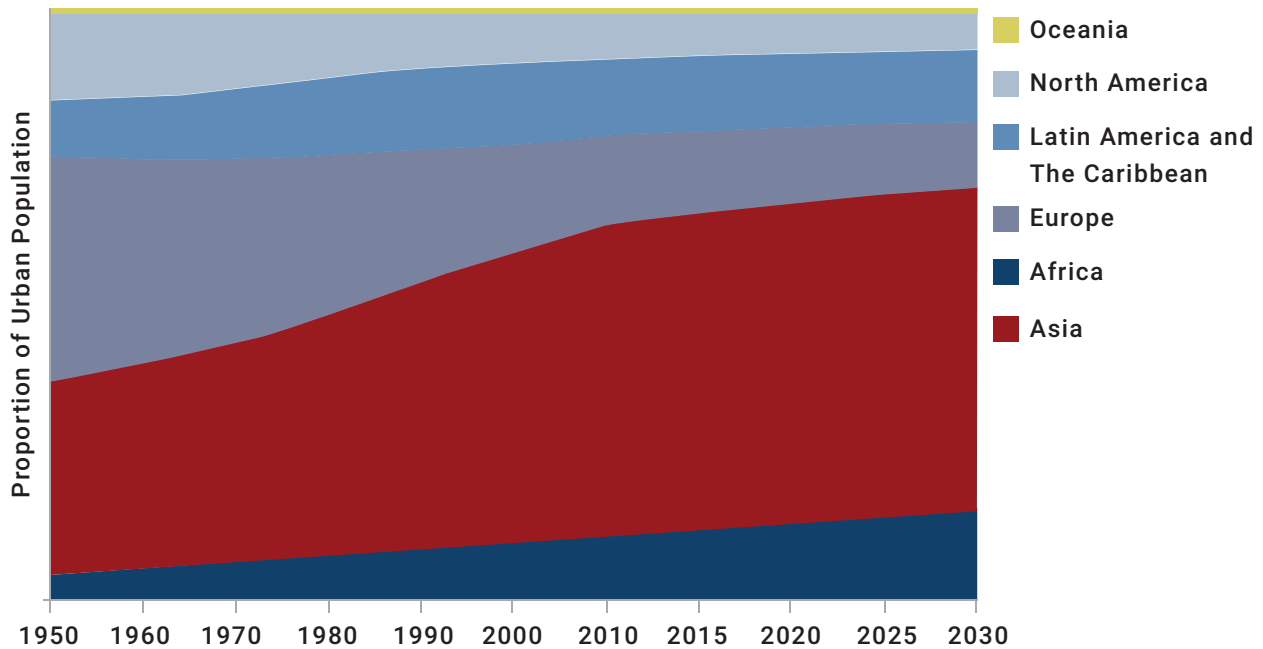
With its large treatment-naïve population, highly skilled investigators, robust clinical infrastructure, faster time to recruit patients, cost efficiencies and the same high-quality output, Asia has emerged as a preferred outsourcing destination.

Resources and Capabilities

1. Vast patient populations

Urban population¹⁵

Urban populations globally have grown from 746 million in 1950 to 3.9 billion in 2015; they are expected to hit roughly 5.0 billion by 2030. Asia is home to 53% of the world's urban population, and its urbanization rate is highest, increasing by 1.5% per year compared to Western countries that are growing at less than 0.4% annually. By 2030, 58% of the urban population is likely to be concentrated in Asia. Figure 3 illustrates shifts in urban population by region from 1950 to 2030.

Figure 3: Proportion of Urban Population by Region, 1950-2030F

Note: F: Forecasted;

Source: 2014 Revision of World Urbanization Prospects, United Nations, accessed 26 August 2016

The number of megacities (cities with populations of more than 10 million) has almost tripled since 1990 - from 10 with a total population of 153 million to 28 with a total population of 453 million in 2014. Approximately 54% of these cities are in Asia, including Tokyo (37 million), Delhi (25 million), Shanghai (23 million), Beijing, Manila and Seoul.

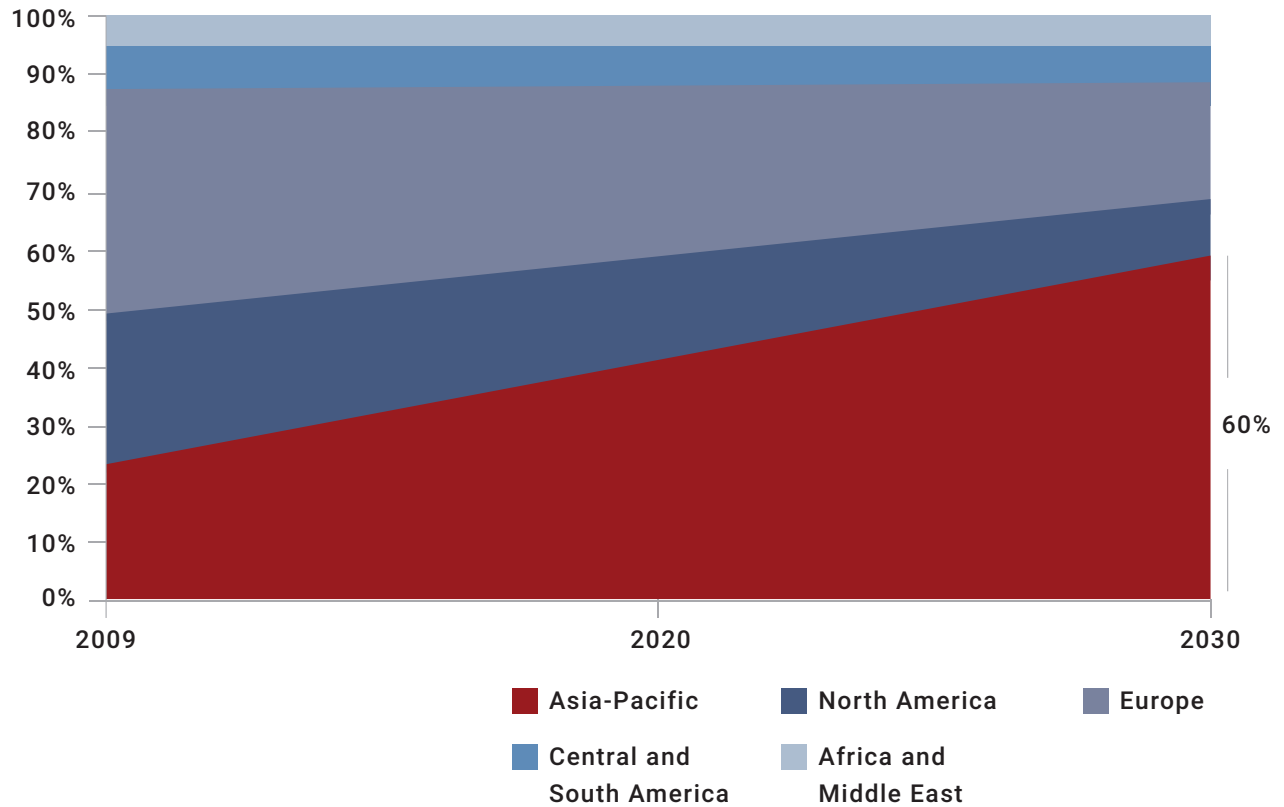
Emerging middle class¹⁶

In 2009, the world's middle class included 1.8 billion people, of which 525 million lived in Asia. The middle class is forecast to grow to 3.2 billion by 2020 and to almost 5.0 billion by 2030. Asia's share of this population will increase from 28% in 2009 to 66% in 2030; middle class consumption in the region will grow from 23% of the global total to 59% over the same period. Middle class consumption projections through 2030 are shown in Figure 4.

The emerging middle class in developing nations plays an increasingly vital role in economic and social development and serves as a potential growth engine. By 2030, 4 of the top 5 emerging markets in the world will be in Asia: China, India, Indonesia and the Philippines are projected to hold the best middle-class potential due to their strong income growth¹⁷.

Rising disposable incomes and health awareness in Asian countries makes the region an important consumer market, warranting early engagement by biopharma companies at the clinical trial stage.

Figure 4: Middle Class Consumption Share by Region, 2009-2030F



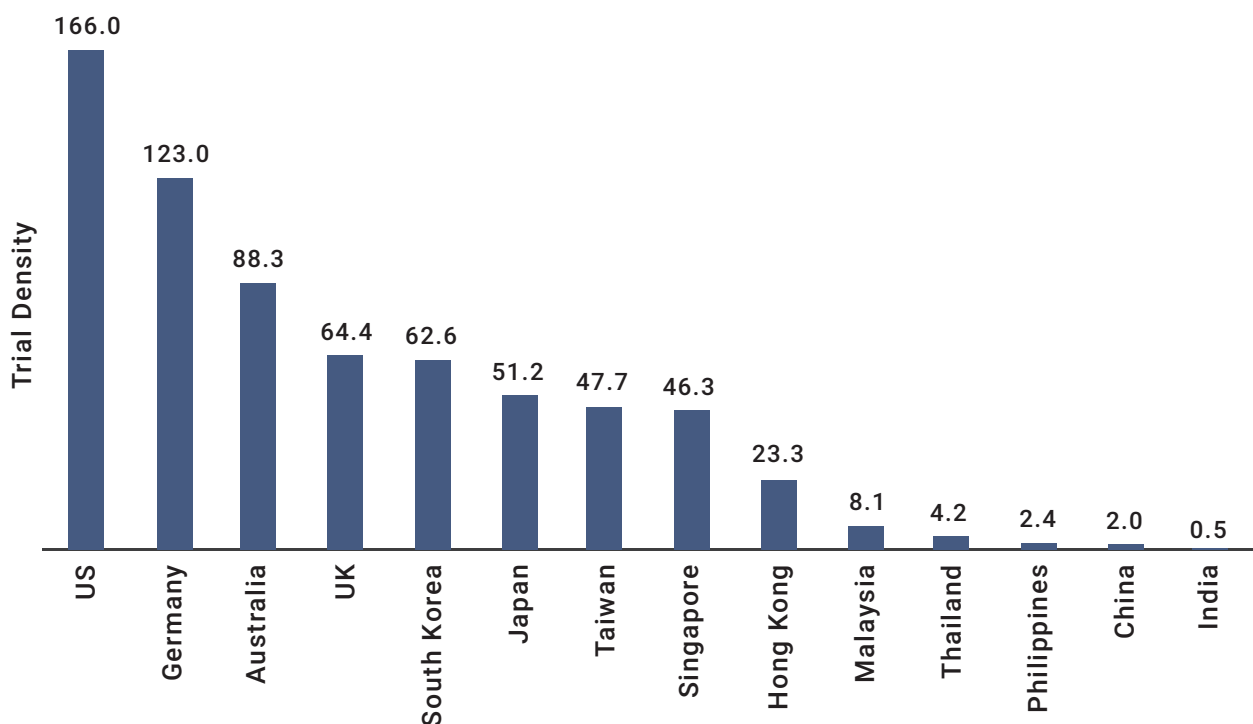
Note: F: Forecasted;

Source: OECD Development Centre, Homi Kharas, *The Emerging Middle Class in Developing Countries* 2014

Treatment-naïve populations

Asia possesses a large, concentrated patient pool ideal for the speedy recruitment of trial subjects. The large treatment-naïve population, especially in Japan, Malaysia, Thailand and China, presents a significant opportunity. Figure 5 shows the density of clinical trials in selected countries in 2016.

Figure 5: Clinical Trial Density in Selected Countries, 2016



Note: Trial density is the number of recruiting sites for Industry initiated trials on April 14th 2016 divided by the country population in millions

Source: ClinicalTrials.gov, Methodology as per: Trends in the globalization of clinical trials, Fabio A. Thiers, Anthony J. Sinskey & Ernst R. Berndt, Nature Reviews Drug Discovery 7, 13-14 (January 2008)

Case Study: High Recruitment Rate¹⁸

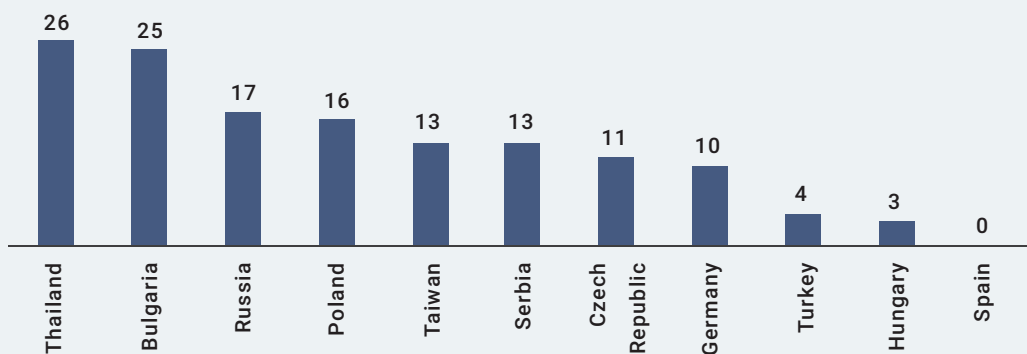
Background

A Swiss biopharma company conducted Phase III studies for acute inner ear hearing loss across 80 sites in Bulgaria, Czech Republic, Germany, Hungary, Poland, Russia, Serbia, Spain, Taiwan, Thailand and Turkey.

Study Results

Despite the high screen failure rate, Thailand was able to recruit the highest number of participants among the countries.

Figure 6: Patient Recruitment Number, by Country



- Approximately 90% of sites in Thailand recruited at least one patient while the average in all other countries was 57%, resulting in 3 sites being added in Thailand.
- High compliance with case report form completion.

Depending on the indication, Asia has several large patient pools concentrated in major sites. For example, we initiated studies targeting chronic hepatitis patients in a few sites in South Korea and Thailand and recruited many patients from just those sites. This enabled us to achieve faster recruitment and obtain quality data.

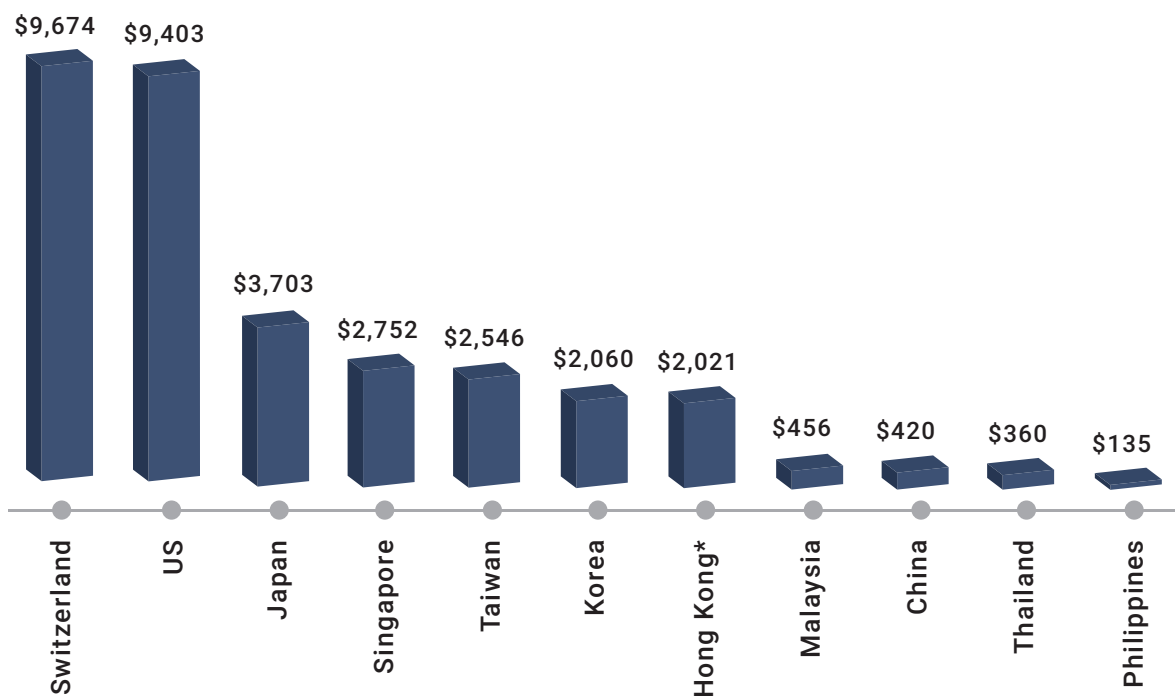
Paul Gineste, Clinical Operations Director, Abivax



Government Spending¹⁹

Per capita government spending on healthcare in Asian countries is lower than in the US and Western Europe. For example, Thailand's healthcare spending per capita in 2014 was \$360, while in the US it was \$9,403. Annual spending in Vietnam, Indonesia, and the Philippines was lower than \$140. Clinical trials are an effective way for Asian patients to get access to innovative therapies given governments' relatively low healthcare spending. Per capita healthcare spending by selected countries in 2014 is shown in Figure 7.

Figure 7: Per Capita Government Healthcare Spending by Country, 2014



*2013 data

Source: The World Bank, health expenditure per capita (current US\$) 1995-2014, accessed 4 August 2016; export.gov; dh.gov.dk 2016 Health Facts Edition.

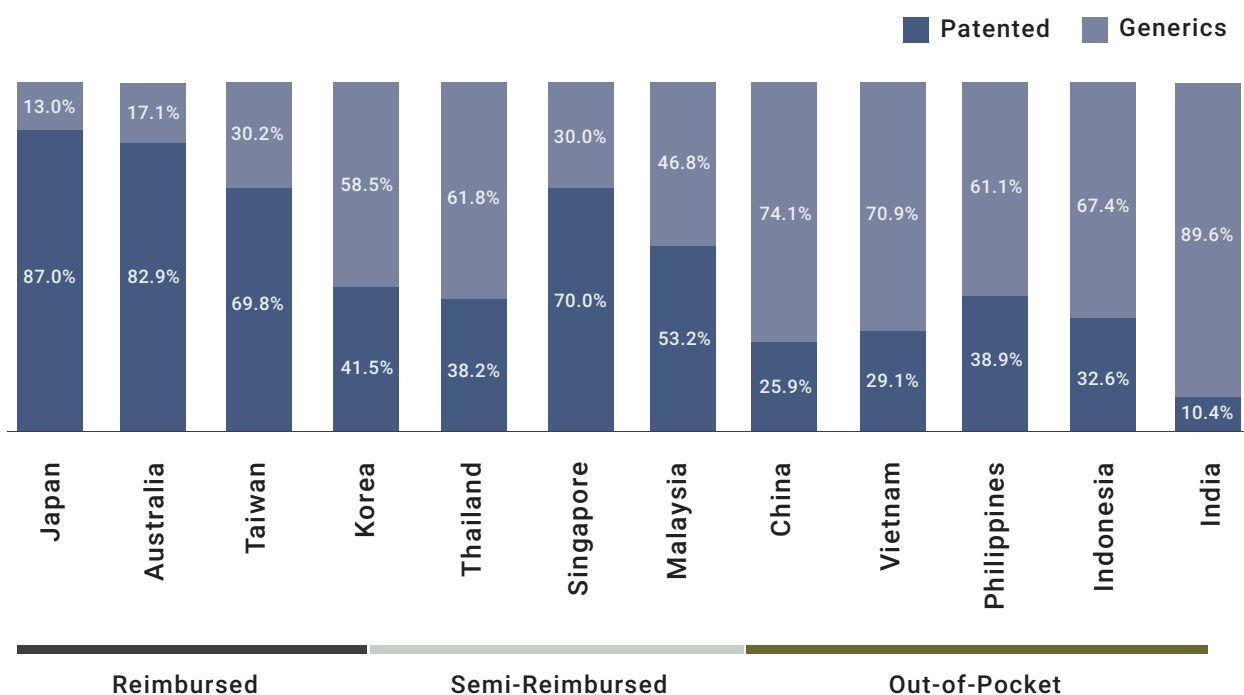
The medical systems in many countries in Asia don't pay for certain drugs for patients, which makes the patient look at clinical trials to get access to best medical care and an opportunity to cure their disease. This was a great advantage for us.

Bruce Given, Chief Operations Officer, Arrowhead Pharmaceuticals



Consumer spending on generics compared with patented drugs is driven by gross domestic product (GDP) per capita and the reimbursement level of the country, as illustrated in Figure 8.

Figure 8: Estimated Prescription Sales Breakdown by Country, 2015



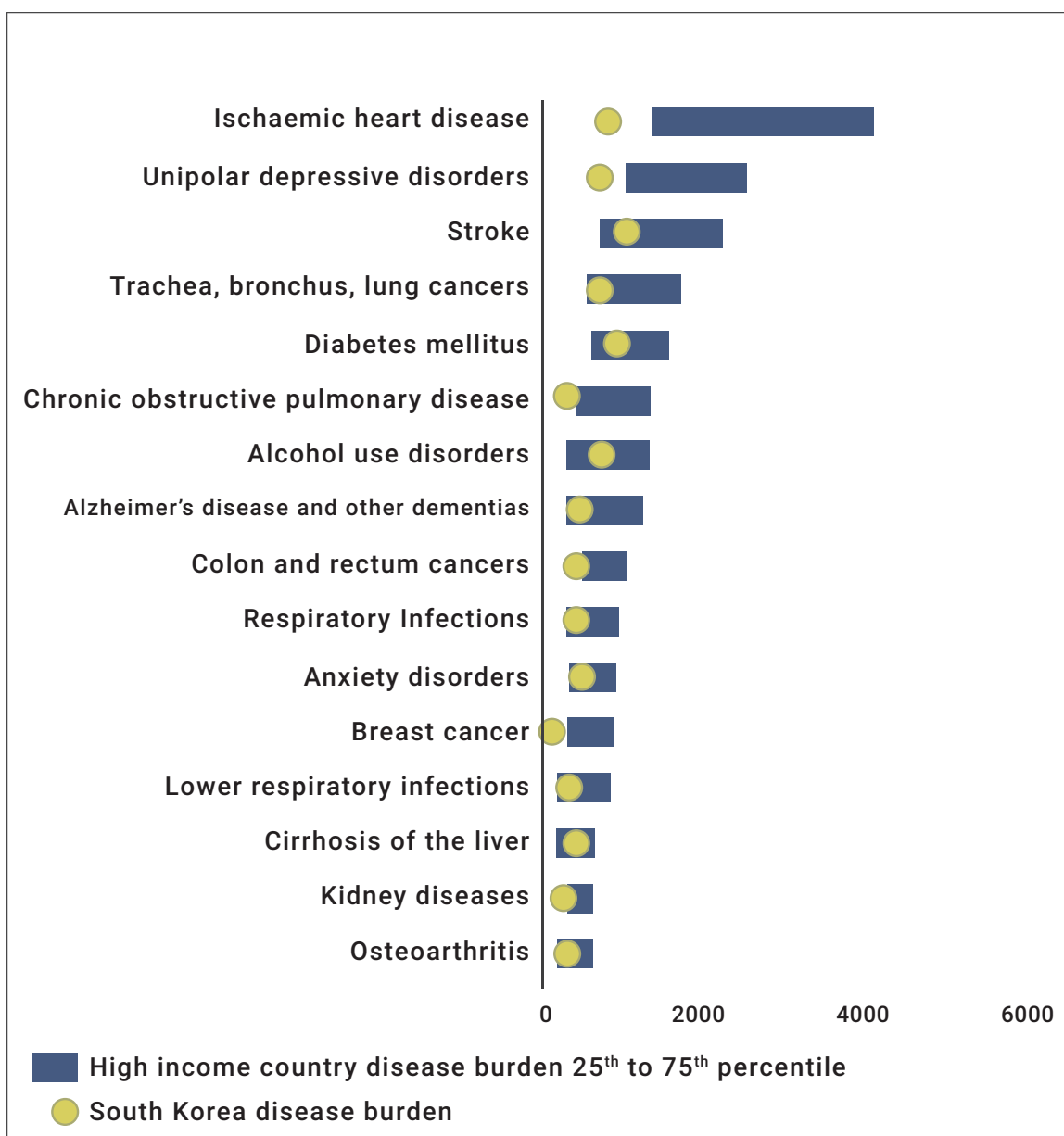
Source: Pharmaceuticals & Healthcare Report, All Asian Countries, Q1 2015, Business Monitor

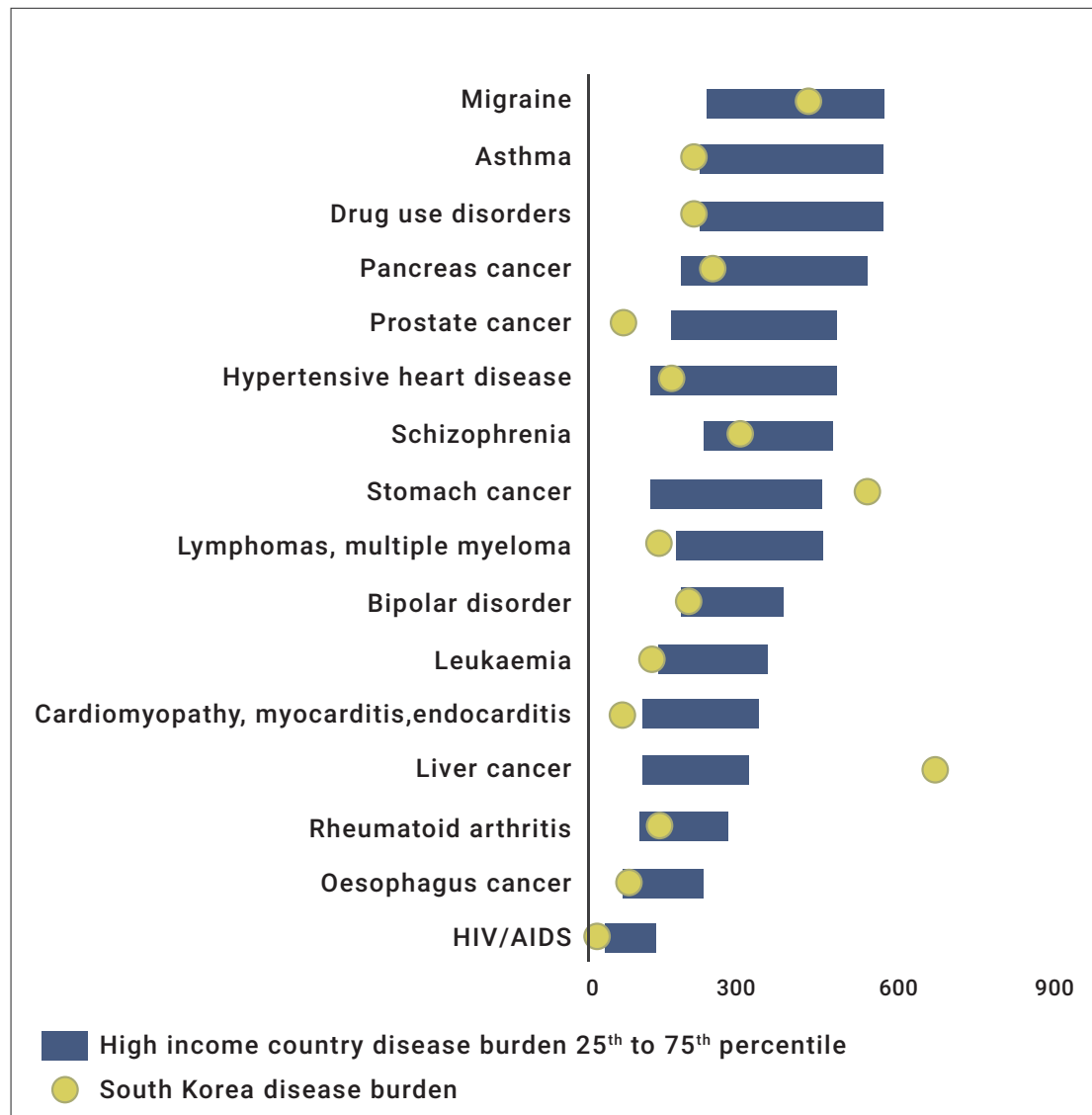
2. Diseases and Treatment Options

Disease patterns similar to the West²⁰

Asian countries are beginning to show similar or higher incidence rates of major diseases to Western nations, providing a comparable environment to conduct clinical trials. South Korea, as an example, is illustrated in Figure 9.

Figure 9: South Korea Disease Burden vs. High-Income Countries*, Disability-Adjusted Life Years, per 1000 population





*As defined by World Bank.

Source: World Health Organization; Novotech

While most disease patterns in Asia increasingly mirror those of Western countries, certain conditions show particular spikes in prevalence, such as gastric and esophageal cancer in China, liver cancer in South Korea, and hypertensive heart disease in Philippines²¹. The high incidence and prevalence of certain diseases in Asian countries make the region extremely attractive for conducting clinical trials, given the shortage of patients in US and Europe for these diseases.

Therapeutic area expertise

Many Asian countries and sites are global leaders in relevant therapeutic areas. The National Taiwan University (NTU) Hospital is a leading facility for cardiovascular treatments and carried out more than 500 heart transplants as of 2014 with a success rate exceeding 90%²². NTU's College of Medicine specializes in cancer research and clinical trials for novel drugs in parallel with Western countries.²³

Japan, China, Singapore and South Korea are front-runners in stem cell therapy due to market-friendly government regulations and significant funding. China alone has 17 academic institutions and hospitals that contribute to regenerative medicine research, with 72 ongoing trials. Japan has conditional marketing approval options for regenerative medicines²⁴, creating growth opportunities and placing Asia on the world's clinical trials map.

Availability of KOLs

Asia has knowledgeable KOLs and experts across many therapeutic areas. Many KOLs are global experts in their field, and their inclusion in trials is extremely beneficial. A number of Asian KOLs have been part of the World Health Organization's Technical Advisory Board and published papers in reputable medical journals. The percentage of citable medical journal articles that came from Asia grew from 19% in 2005 to 25% in 2015. China alone demonstrated a 150% growth in citable articles during this period²⁵.

We worked with highly knowledgeable investigators and KOLs from academic institutes in Asia. They were enthusiastic, professional, and committed. We did not face any major quality issues; the data quality was extremely good.

Josianne Nitcheu, Senior Project Manager, Abivax



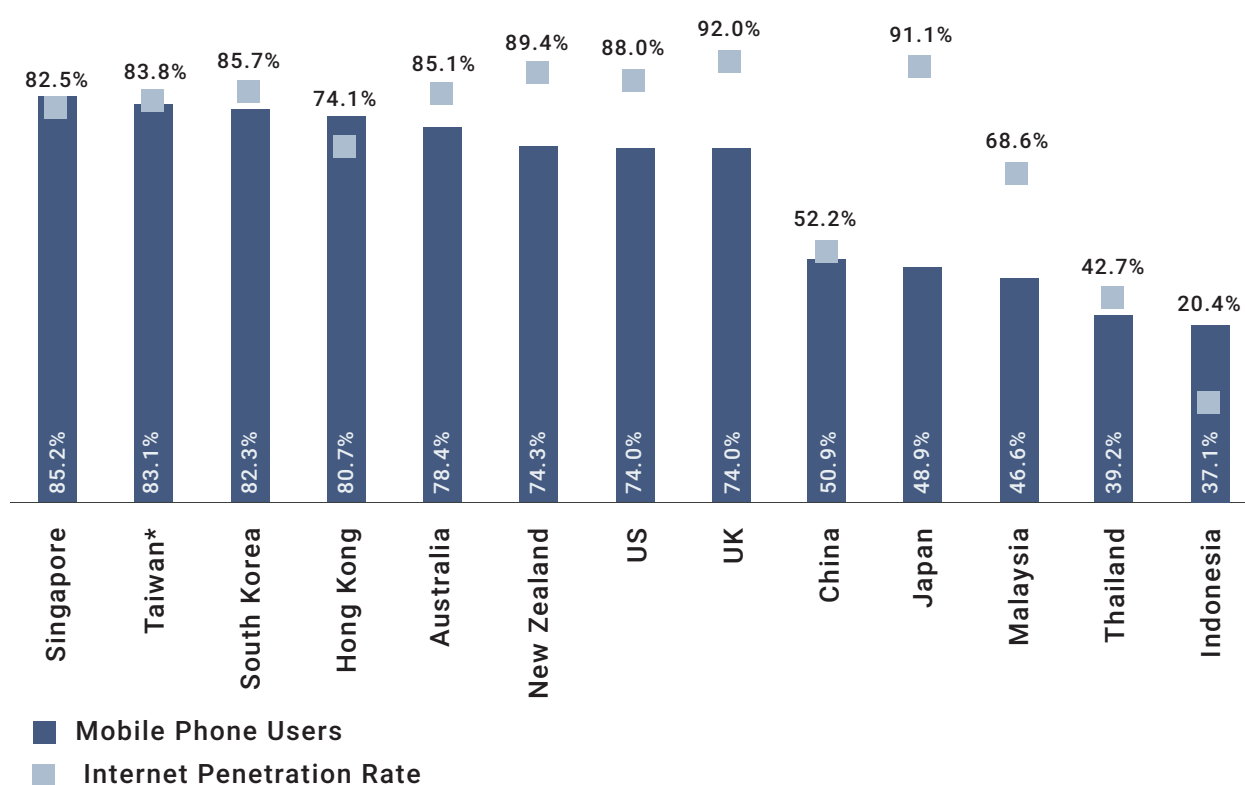
3. Infrastructure

Mobile and Internet penetration

In 2015, Asia-Pacific boasted more than 1.0 billion smartphone users. The number of users is expected to increase at an annual rate of 7% through 2019. Smartphone adoption in 2015 among mobile phone users was 40.8%; it is likely to increase to 51.5% by 2019. China alone accounts for 28.3% of all smartphone users globally²⁶. South Korea also is technologically advanced and digitally connected: Almost 80% of South Koreans own a smartphone; penetration is even higher among those aged 18 to 24, at 97.7%²⁷.

Japan's 2016 Internet penetration rate of 91.1% was higher than at the United States' 88%; while South Korea, Taiwan and Singapore mirror Western nation standards. The percentage of mobile phone users and the Internet penetration rates of selected countries are shown in Figure 10.

Figure 10: Percentage of Mobile Phone Users (2015) and Internet Penetration Rate (2016), Selected Countries



* 2014 data from Internetworldstats.com

Source: Asia-Pacific Boasts More Than 1 Billion Smartphone Users, September 2015; eMarketer, May 2015; Global Internet Penetration Rate, January 2016, accessed 9 August 2016

Specialized clinical trial centers in Asia

Asian countries are aiming to become more competitive by building appropriate site experience, technological expertise, infrastructure, and scale to manage large clinical trials.

Large hospitals in the region, such as the Chang Gung Memorial Hospital in Taiwan with 9,000 beds and serving 28,000 outpatients a day, offer massive scale for clinical trials. By comparison, the largest US hospital New York Presbyterian University Hospital has 2,478 beds. China boasts at least 16 public hospitals with more than 3,000 beds each²⁸. St Mary's Hospital in Seoul has 6,000 beds and the Asan Medical Center, also in Seoul, has more than 2,700 beds, serving 11,000 outpatients on average per day²⁹. South Korea provides extensive healthcare services and is home to more than 93,000 practicing clinicians, 3,600 hospitals, 43 teaching hospitals, and about 60,000 clinics³⁰.

Some South Korean and Japanese hospitals not only have the latest equipment, technology, and infrastructure, but also maintain a de-identified patient and trial database. One example is South Korea's SCI-Consortium, which includes 4 leading hospitals, 1,545 investigators, 177 dedicated beds for clinical pharmacology studies, and 30,000 active patients enrolled in clinical studies. The SCI-Consortium has developed a clinical data retrieval system that enables queries of clinical data from more than 10 million de-identified records derived from inpatient and outpatient care activities and provides precise information to find eligible patients for clinical trial research. The system allows much faster recruitment of either patients or healthy volunteers³¹.

We conducted a feasibility study for a global CRO who was looking for patients with very specific inclusion and exclusion criteria. We were recruiting for Type I diabetes-associated nephropathy in Phase IIa. The need was for adults between the age 20 to 50 years, with type 1 diabetes mellitus for ≥ 8 years, lab result of $\leq 11.0\%$ HbA1c and excluding patients on non-insulin antidiabetic medications. Within 5 days, we were able to scan our database to identify 28 patients through our 3 hospitals' endocrinology departments. The database not only helps identify patients rapidly, but also helps assess the eligibility design and feasibility.

*Dong-Kyu Kim, Secretary General,
SCI-Consortium of Clinical Trials Centers at University Hospitals*



Rising adoption of electronic health records (EHRs)

Several Asian countries are adopting EHRs and utilizing digital technologies to go paperless. South Korea is a leader in building IT capability to provide online access to health information, though not mandated by the government. A 2014 study cites EHR adoption of more than 80% in tertiary hospitals³². The Seoul National University Bundang Hospital was the first non-US hospital to achieve the HIMSS Analytics Stage 7 standard for highest electronic medical record adoption. This hospital is fully digital, with all medical data and records on its server³³.

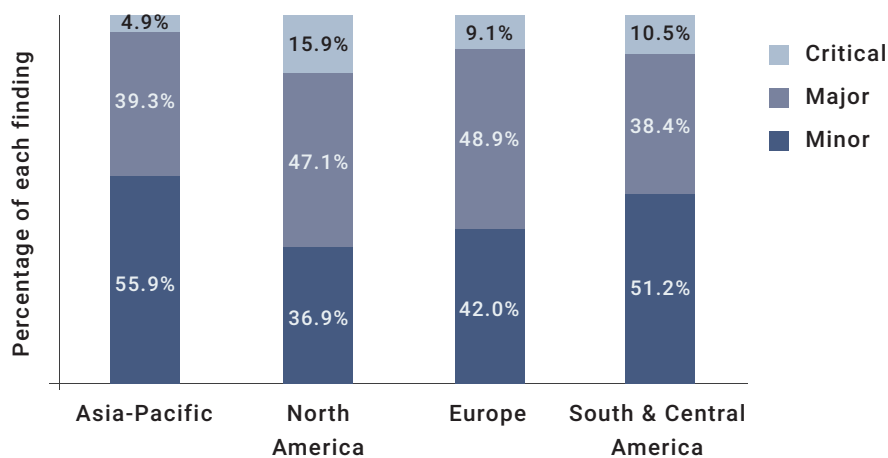
China is also expanding its EHR adoption, with 50% of tertiary hospitals, 30% of urban health centers, and 20% of rural hospitals using EHR systems as of 2014. The adoption rate is likely to reach 80% in tertiary hospitals by 2020. The Chinese government plans to implement EHRs in at least 50% of urban clinics and rural hospitals over the same period³⁴. Hong Kong's government intends to increase EHR adoption to 60% by 2019-2020 from the current 30%, approaching the US adoption rate of 69%³⁵.

Worldwide Data Acceptability

1. Low rates of Regulatory Findings

The percentage of critical EMA Good Clinical Practice (GCP) inspections in the Asia-Pacific region was less than in other regions, as shown in Figure 11, and the percentage of major findings was among the lowest. Similarly, the percentage of official actions taken in FDA inspections was also lower than North America, as shown in Figure 12, reflecting the high quality of international compliance.

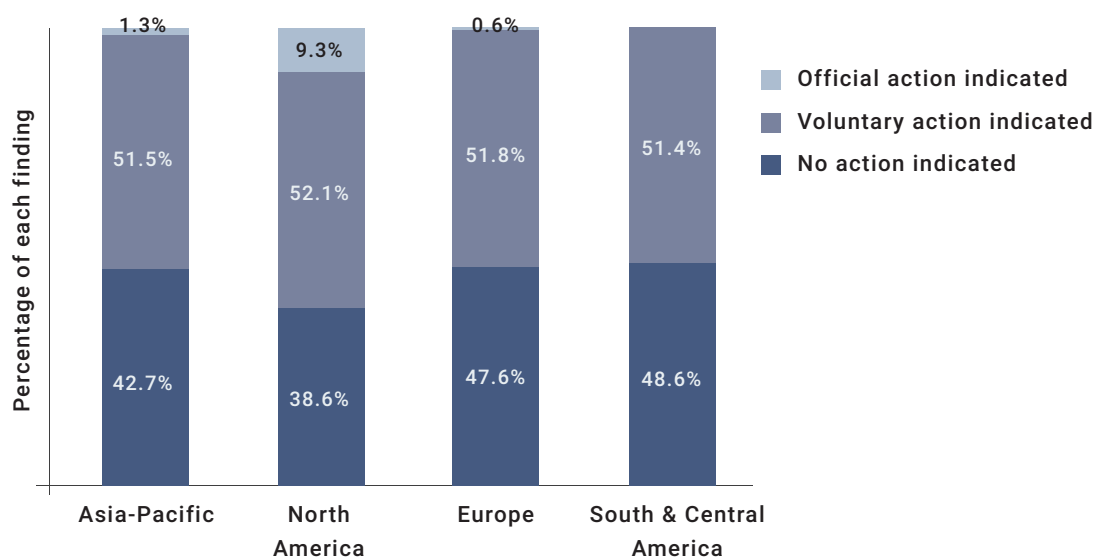
Figure 11: EMA Inspections by Type, 2000-2012



Note: Latest country split data available for 2012

Source: Classification and analysis of findings from GCP inspections conducted at the request of The Committee for Medicinal Products for Human Use (2000-2012), December 2014, EMA

Figure 12: US FDA Inspections by Type, 2000-2015

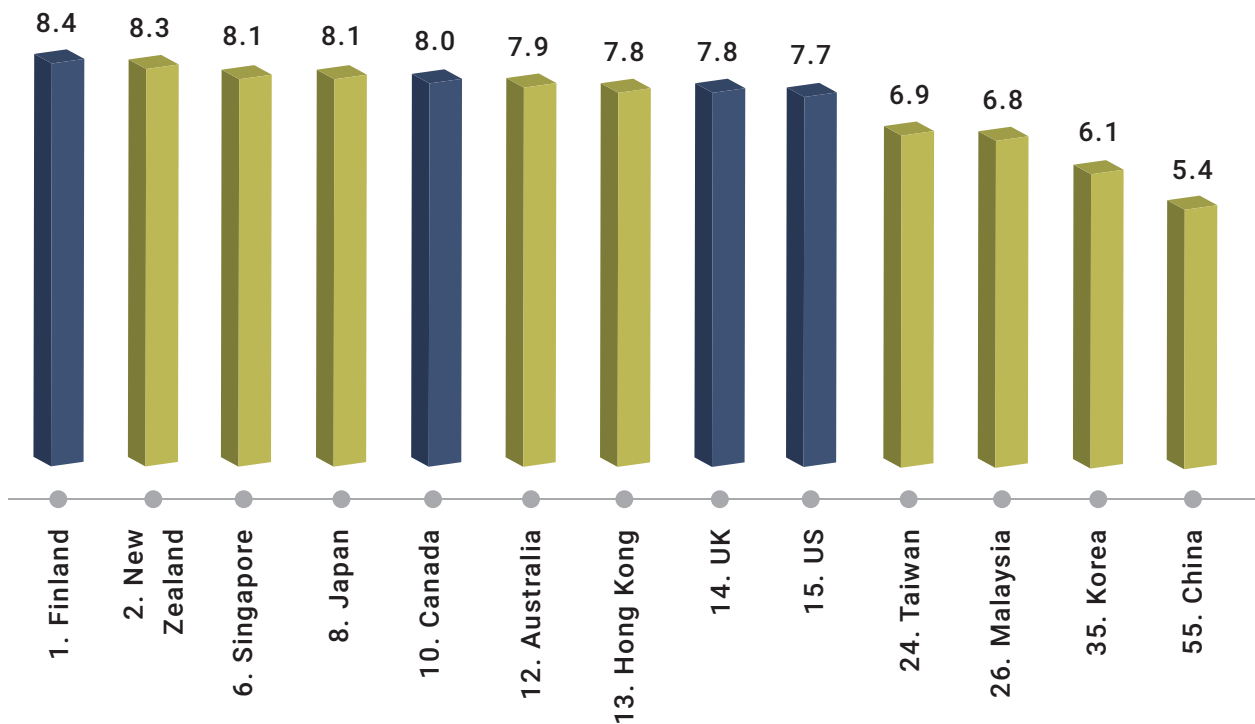


Source: Inspections Database, US FDA.gov website

2. Strong Intellectual Property (IP) rights protection³⁶

IP rights in Singapore and Japan are consistently ranked among the top 10 most secure out of 128 countries. The United Kingdom (UK) and US are 14th and 15th, respectively, alongside some European countries. Figure 13 shows the IP Rights index of selected countries.

Figure 13: IP Rights Index*, Global, 2016



**The IP Rights Index comprises protection of IP rights, patents, and copyrights. It compares 128 countries.*

Source: The International Property Rights Index 2016, accessed 23 August 2016.

Over the past decade, China has continued to strengthen its IP protection process to meet global standards, while enforcing its legal framework and enhancing public awareness. In June 2015, China and the US signed an agreement to work together on IP rights violations as part of efforts to prevent the export of counterfeit pharmaceutical products³⁷.

Case Study: Data Quality and Fast Recruitment³⁸

Background

A US biotechnology company developing therapeutics targeting devastating diseases, primarily cancer, engaged Novotech, an Asia-Pacific based CRO, to conduct a Phase III study in biomarker-positive patients in Australia, New Zealand, India, Taiwan and Thailand. The sponsor also had study sites in North America, Latin America and Europe.

Challenge

There was no definite data on the number of patients globally for this biomarker. During recruitment for the trial, the screen failure rate was 73%, confirming that only a small percentage of the patient segment was eligible for the study.

Benefits

Despite the high screen failure rate, the Asia-Pacific sites continued screening patients and remained highly engaged in the study.

- Target patient enrolment in Asia-Pacific was achieved well in advance of the planned timelines and enrollment.
- Data quality was 155% higher than all other sites.
- Asia-Pacific was the first and only region to achieve 100% survival data sweep, 100% data entry, and zero open queries, all within timelines.
- Despite having 26 sites across Asia-Pacific, the issues encountered were minimal.

We always include Asia-Pacific sites in our global trials and are impressed by the quality of education, care to patients and commitment to R&D at these locations. The regulatory activation times have been in line with Western countries and recruitment rates have exceeded our expectations. Even the data quality was exemplary in terms of number and time to address the queries.

Associate Director, Clinical Trial Management, US Biotechnology Company

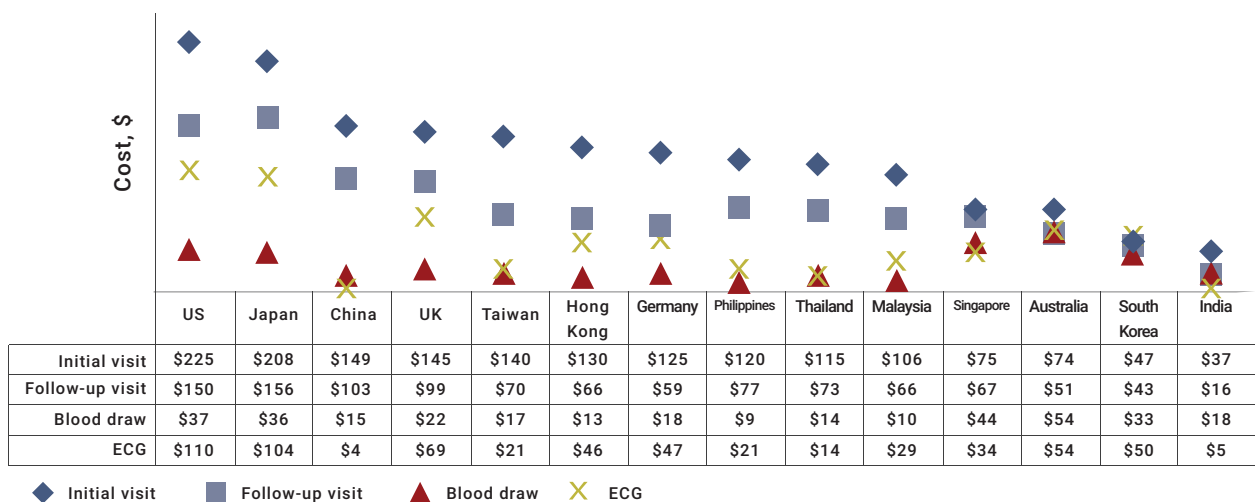


Cost-Efficiencies

1. Cost-competitive

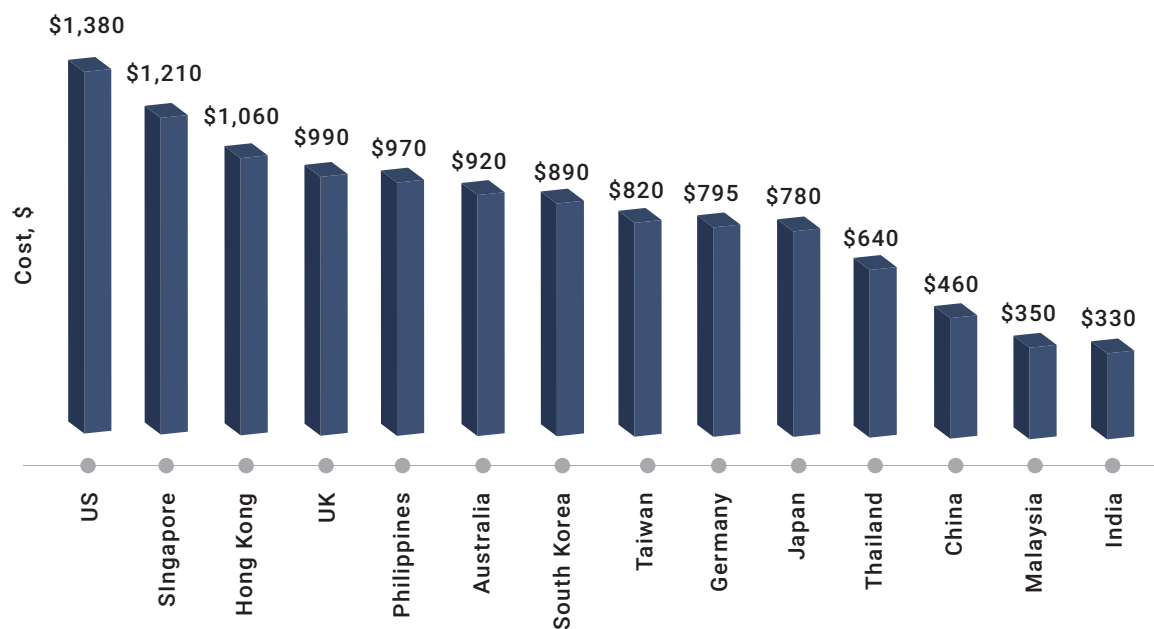
Low operational costs positions Asia as a highly attractive destination for clinical trials when compared with the US and Western Europe. Recent data provided by Medidata Grants Manager indicates that doctor visits, medical treatments and procedures tend to cost less in Asian countries, as shown in Figures 14 and 15. For example, an ECG procedure in the US with interpretation and report costs around \$110 on average. The same report would only cost \$4 in China.

Figure 14: Cost Comparisons of Visits and Tests, Selected Countries, 2016



Source: Medidata Grants Manager, Cost Comparisons 2016

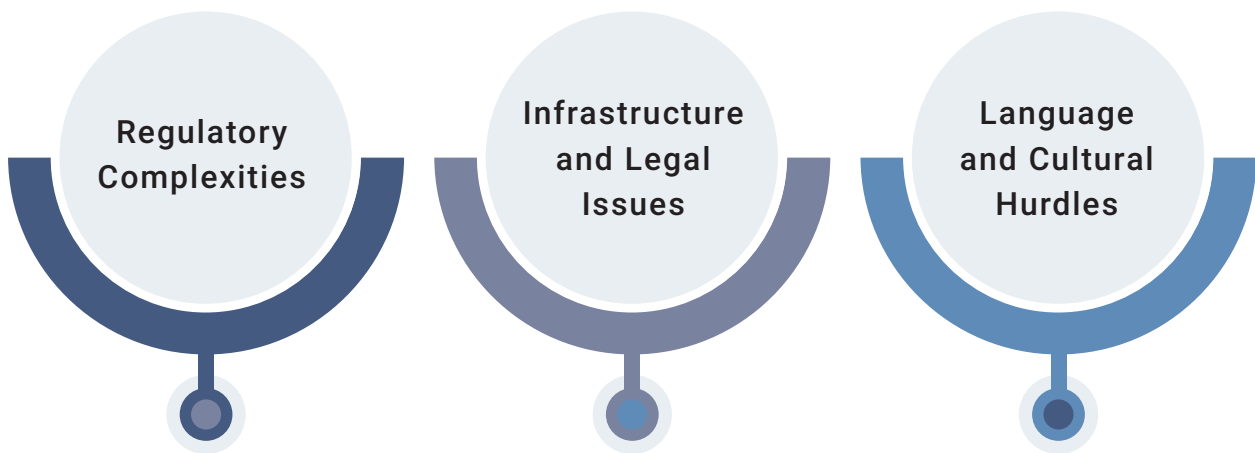
Figure 15: Cost per Patient per Visit, All Therapeutic Areas and Phases, Selected Countries, 2016



Source: Medidata Grants Manager, Cost Comparisons 2016

Key Challenges of Clinical Trials in Asia

While the globalization of clinical research is driving growth in Asia, there are a few challenges relating to regulatory complexities, infrastructure and legal issues, and language and cultural hurdles.



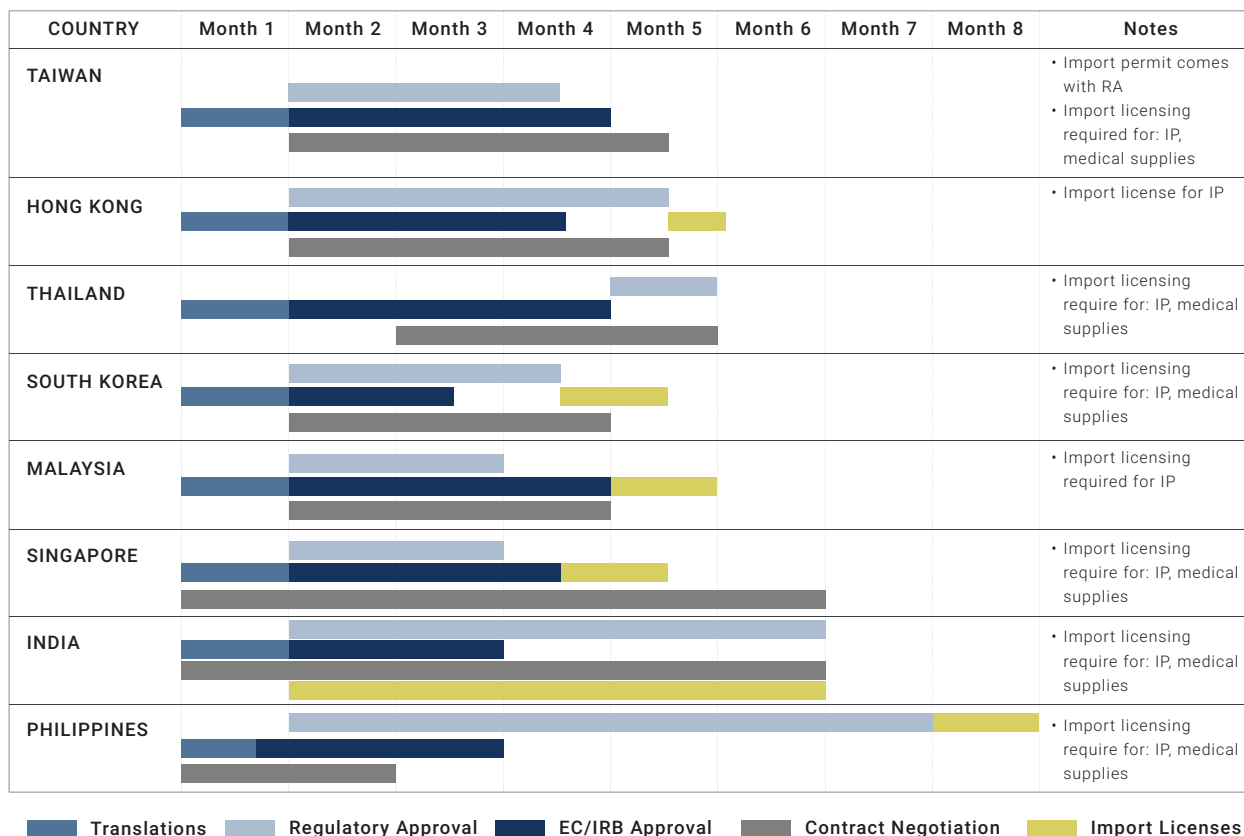
Regulatory Complexities

1. Engagement and timelines^{39,40,41}

Undertaking clinical trials in Asia requires an appreciation that the regulatory regimes are heterogeneous. The Institutional Review Board (IRB) approval, regulatory, import licensing and contract negotiations are undertaken simultaneously in some countries, while others carry them out separately. Asian countries also have varying requirements for local language translation, import or export licensing, and data on local patients.

Many countries in Asia have regulatory approval timeframes that are competitive with Western countries, and more streamlined to ensure timely and predictable regulatory approvals as shown in Figure 16.

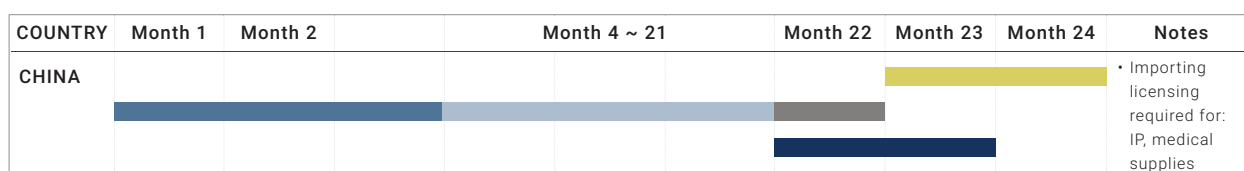
Figure 16: Regulatory Timelines, Selected Asian Countries



Source: Novotech

Regulatory approval timeframes in China remain long, as shown in Figure 17, although the Chinese regulators have implemented a number of initiatives to improve the approval times.

Figure 17: Regulatory Timelines, China



Source: Novotech

2. Standard of care:

In the US, Europe and Australia, standard of care is generally provided by the patient's normal payer during a clinical trial. This may be the relevant government agency or the patient's insurer. In most Asian countries however, sponsors are required to pay for the standard of care. This is even the case in health systems with high levels of government support such as Korea, Japan and Taiwan.

- In Taiwan, Japan, China, India, Singapore and Malaysia, sponsors are expected to pay for the standard of care with few exceptions.
- In the Philippines, patients are still able to access national insurance for standard of care but coverage is generally low and so sponsors are expected to cover out-of-pocket costs.
- In Hong Kong and Thailand, there are no formalized requirements and payment will often be a negotiation between the trial site and the sponsor.
- In Korea, the sponsor is generally expected to pay for standard of care, although the government has proposed legislation to allow national insurance coverage to improve Korea's clinical trial competitiveness.

Nevertheless, total cost of running studies in Asia, continues to provide cost savings in the region of 30% to 40% as compared with the US and Western Europe.

Infrastructure and Legal Issues

1. Infrastructure barriers in some area

Asia's R&D and infrastructure is mostly concentrated in wealthier metropolitan cities. While there has been significant progress in technology adoption for use in hospitals and patient services, there may be infrastructure issues in smaller cities or fast growth cities with insufficient infrastructure investment. Technology dependent data capturing methods and backup infrastructure may need to be planned.

2. Logistics complexities in megacities

Megacity growth rates have resulted in traffic congestion in a few Asian cities. Road transport logistics must therefore be planned in advance in some Asian cities to ensure diagnostic samples or investigational products are not compromised⁴². CRO vendors need to have different approaches for time-sensitive transportation, such as multiple drug depots or temperature-controlled couriers to ensure crucial patient samples or drugs are not affected in transit.

3. IP protection⁴³

Asian governments have created a more robust IP protection system over the last few years. India and China have made substantial improvements in IP legislation alongside efforts to digitize operations and hire additional staff. China has defined a long-term IP rights strategy, with the overall goal to become an innovation economy by 2020, as stated in its 2011 Five-Year Plan. The government of Indonesia has also launched policy statements and actions for IP protection.

Language and Cultural Hurdles

1. Local languages and English variability:

Most Asian countries use and understand English, although they primarily use their local language for communication. Since English is the most commonly used language in global research, many Asian countries require translation of trial documentation, although in some countries this may only apply to patient materials. English proficiency varies across Asia with slight differences in word usage, meanings and accents, so documentation translation should be done with local experts. Many sponsors will want to invest in back-translation from the local language to English to ensure that the meaning of critical documents is preserved.

2. Cultural norms:

- **High value in 'saving face':** Professional position, gender and age play a major role in many Asian cultures. Maintaining a good reputation at the workplace and creating an individual and community view is also important. Many of these factors contribute to the norm of 'saving face', which is pivotal in business negotiations, and in developing and maintaining relationships. For example, it is helpful to have senior staff members communicate non-compliance to principal investigators, and junior employees to submit improvement ideas via process-based templates in order to avoid uncomfortable hierarchical conflict between junior and senior staff.
- **Belief systems:** Asia is a heterogeneous region; several nations have multiple ethnic groups, religions and belief systems. Vendors should have a good understanding of different cultural beliefs during the planning of clinical trials because these could affect patient recruitment and retention. For example, Chinese New Year and Ramadan festivals in Southeast Asia are widely celebrated and could impact trial schedules. Certain countries also require submission of information about products sourced from animals because of religious beliefs and social customs. Malaysia, Indonesia and the Philippines, for example, require information about all ingredient sources. Indonesia does not approve any product containing porcine materials.
- **High trust in physicians:** Patients in Asia respect doctors and rely on their guidance in determining medical treatments. Physicians play a vital role in recruiting patients in these nations, and this high level of trust may contribute to low levels of patient attrition.
- **Perceptual reporting:** Many Asian cultures have differences in the way they report pain, moods and emotions e.g. depression, mania and anxiety. Validated cultural equivalence surveys may therefore be important in the design and analysis of certain trials.

3. Local medical practice and traditional medicines

Cultural diversity in the practice of medicine may affect trial execution and results. For example, it is important for investigators to record the concurrent use of Chinese traditional medicines or alternative therapies such as Ayurveda as they have the potential to influence study results.

4. Gift giving

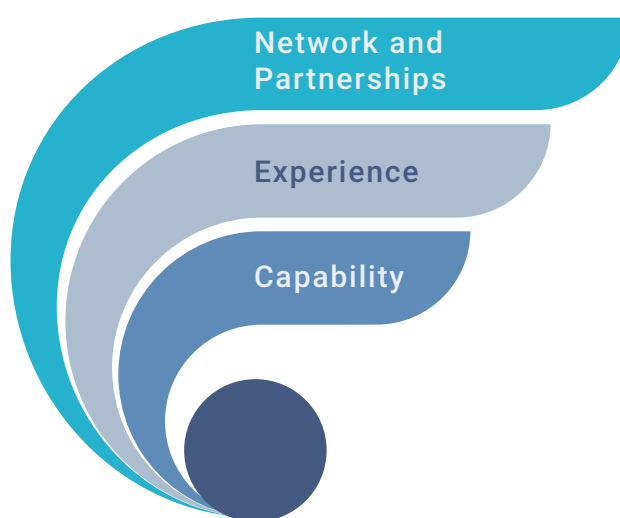
Modest gift giving is a common practice in business in a number of Asian countries including South Korea, Thailand and China. Western companies must ensure that they comply with their global standards by establishing clear policies for modest gift limits and filing internal gift disclosures.

5. Informed consent

Asians tend to be family and group-oriented, placing a strong emphasis on family connections, especially during hardship. Treatment decisions, including trial participation, may require broader discussion with family members before an individual is willing to provide consent⁴⁴.

Critical Factors in Selecting a CRO for Clinical Trials in Asia

The key factors biopharma sponsors should consider when selecting a CRO include relevant clinical capabilities, language proficiency, technological expertise, experience in the study types and phases, and regional presence and network.



Capability

Sponsors expect CROs to be client-centric, have knowledgeable teams and offer flexibility in the engagement model:

- **Quality talent and training:** A well trained, experienced and competent clinical operations team is critical. Companies expect the CRO team to have in-country senior management to maintain day-to-day site, KOL, PI and regulatory relationships that require personal interaction. Ideally, staff should be full-time employees and maintain a company culture that values quality and customer service, while being sensitive to local environments and needs. They should have rigorous training and performance evaluation parameters to maintain high quality.
- **Regulatory knowledge:** Companies look for CROs that understand the regulatory requirements in the biopharma space. Project managers and their teams should have multi-country experience to be able to plan trials according to regulatory timelines in each country and avoid delays.
- **Extensive US FDA & EMA submissions capability:** US and European companies seek CROs that not only understand local regulations, but have had extensive history of conducting and managing studies for US FDA and EMA submissions.

- **Language capabilities:** CROs should have fluent English-speaking team members as well as local language experts who understand the market. A multilingual workforce is critical to preventing miscommunication or reliance on external translators during client meetings and communications.
- **Advanced technology and systems:** Quality and scalability of IT systems and infrastructure (e.g., standard operating procedures, quality systems) are important. Companies expect vendors to have advanced software such as the clinical trial management system, electronic data capturing systems, trial master files, and market intelligence systems to enable sponsors to monitor project progress and quality and view data online in real time.
- **End-to-end capabilities:** Sponsors also look for integrated service providers that demonstrate capabilities across the entire clinical trial value chain, so they can minimize the number of vendors within a region.

For large clinical trials, we looked for a vendor with local presence in all major Asian countries so they are familiar with the regulations and cultural elements of each Asian site and acts as an end-to-end, full-service CRO.

Paul Gineste, Clinical Operations Director, Abivax



Experience

Companies aiming to conduct clinical trials in Asia seek CROs with expertise in working across multiple jurisdictions and time zones. The vendor should have knowledge across various study types, phases, diseases and therapeutic areas. Experience and expertise in particularly challenging situations such as rescue studies is often advantageous in a complex region.

We wanted to launch the product in a few nations, so we sought a CRO with a presence in multiple countries. Other important factors were cost-competitiveness and reputation of the CRO in the market.

Chief Finance Officer, Chinese-based Pharmaceutical Company



Network and Partnerships

- **Regional presence:** Sponsors look for CROs with an international presence to be able to conduct trials simultaneously in multiple countries. Especially in Asian markets with diverse languages, cultures and regulations, it is critical for the CRO to have a local presence in each country with a good understanding of the unique challenges of each area.
- **Flexible approach to multi-CRO engagements:** CROs need to demonstrate flexibility by working with other regional specialist CROs which may include adopting their SOPs and systems. Sponsors may wish to adopt a variety of approaches which may result in a CRO being the global lead, the regional specialist or on an equal footing with multiple CROs reporting directly to the sponsor.
- **Relationship with investigators and KOLs:** Companies need CROs that foster relationships with the lead investigators, KOLs and institutions. CROs should have affiliations with physician associations across a variety of therapeutic areas.

We were led to our CRO partner by the key investigators in Australia and New Zealand.

For us it is extremely critical that the CRO is familiar with the local regulatory environment and has good working relationship with investigators and local vendors.

Novotech was clearly the first name that we heard in Asia-Pacific and they are extremely focused with extensive reach and clear approach. We were very impressed.

Bruce Given, Chief Operation Officer, Arrowhead Pharmaceuticals



It is important for the CRO to have a presence in any region we execute a clinical trial to ensure an understanding of the culture, regulations and patients we are targeting. Choosing a CRO with existing site relationships is also important in our partnership decision.

Associate Director, Clinical Trial Management, US Biotechnology Company



Last Word

Asia is quickly becoming a clinical research powerhouse facilitated by the availability of a vast treatment-naïve patient pool, superior clinical infrastructure and talent, and low cost. Disease incidences that mirror rates of Western countries create an attractive environment for conducting trials. Government spending on healthcare in Asian countries is relatively low compared to the US and Europe, so clinical trials help patients gain access to innovative therapies. Asia has large, state-of-the-art clinical trial centers that meet patient enrollment and retention goals and generate high-quality data, and are led by skilled investigators. As transparency in the regulatory environment improves, Asia is poised to become the preferred destination for clinical trials.

We highly recommend going to Asia, as we got reliable results, enthusiastic physicians and patients, and experienced KOLs. For us, a good strategy for the US and European companies is clearly to consider Asia for large Phase II and III trials, as it is a very good location to conduct clinical trials.

Paul Gineste, Clinical Operations Director, Abivax



Asia-Pacific is an attractive region to conduct clinical research. The regulatory activation timelines are similar to other parts of the world, while aspects of study execution and standard of care are consistent. Attention to detail in data entry is apparent along with faster response times for query resolution than other regions. Patient costs also tend to be lower than in the US and EU. Additionally, Asia offers favorable recruitment rates.

Associate Director, Clinical Trial Management, US-based Biotechnology Company



References

1. Frost & Sullivan report: Global CRO market, 2015
2. Frost & Sullivan report: Global CRO market, 2016
3. Frost & Sullivan report: APAC Contract Research Organisation (CRO) Market, July 2015
4. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary, <http://www.ncbi.nlm.nih.gov/books/NBK50888/>
5. Rebecca Williams, PLoS, Terminated Trials in the ClinicalTrials.gov Results Database: Evaluation of Availability of Primary Outcome Data and Reasons for Termination, 2015 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444136/>
6. Unger JM et al, Impact of the year 2000 Medicare policy change on older patient enrollment to cancer clinical trials. J Clin Oncol. 2006
7. Venu Menon, 2011, Journal of the American College of Cardiology, International Participation in Cardiovascular Randomized Controlled Trials Sponsored by the National Heart, Lung, and Blood Institute
8. LO Zimmer, Contemp Clin Trials. 2010, International Collaboration between US and Thailand on a Clinical Trial of Treatment for HIV-associated Cryptococcal Meningitis <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2861565/>
9. European Medicines Agency publishes report on patient recruitment and geographical location of clinical trials, April 2013, EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001758.jsp&mid=WC0b01ac058004d5c1
10. Cost of Developing a new drug, Nov 2014, Tufts Center for the Study of Drug Development http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf
11. The New EU Clinical Trials Regulation, 2012
12. Examination Of Clinical Trial Costs And Barriers For Drug Development, July 2014 <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>
13. Clinical trials - Regulation EU No 536/2014, European Commission http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm
14. FDA.gov
15. 2014 Revision of World Urbanization Prospects, United Nations Website <https://esa.un.org/unpd/wup/Publications/Files/WUP2014-Highlights.pdf>
Published 2014, Accessed 26th Aug, 2016
16. Mario Pezzini, An emerging middle class, OECD Yearbook, 2012 http://www.oecdobserver.org/news/fullstory.php/aid/3681/An_emerging_middle_class.html,
Accessed 26th Aug, 2016
17. Top 5 Emerging Markets with the Best Middle Class Potential, Euromonitor International, September 2015 <http://blog.euromonitor.com/2015/09/top-5-emerging-markets-with-the-best-middle-class-potential.html>
18. Novotech Case Study 1

19. The World Bank, Health expenditure per capita (current US\$) 1995-2014, Accessed 4th Aug, 2016 <http://data.worldbank.org/indicator/SH.XPD.PCAP>
20. World Health Rankings, Published 2014, Accessed 30th August 2016
21. Diabetes prevalence, 2015 http://data.worldbank.org/indicator/SH.STA.DIAB.ZS?year_high_desc=false Accessed 30th August 2016
22. <http://www.patientsbeyondborders.com/hospital/national-taiwan-university-hospital>
23. http://irice-ca.mc.ntu.edu.tw/_eng/aboutICECR.php
24. Japan's Take on Regenerative Medicine: Early Commercialization, Early Reimbursement, 2015, Replicel http://replicel.com/recent_coverage/japans-take-on-regenerative-medicine-early-commercialization-early-reimbursement/
25. Country Rankings Analysis <http://www.scimagojr.com/> Accessed 14th October 2016
26. Asia-Pacific Boasts More Than 1 Billion Smartphone Users, eMarketer, September 2015 <http://www.emarketer.com/Article/Asia-Pacific-Boasts-More-Than-1-Billion-Smartphone-Users/1012984#sthash.lsReCJF1.dpuf>
27. More clinical trials are being conducted across Asia, November 2015, BioSpectrum Asia https://www.mdsol.com/sites/default/files/mHealth_Clinical-Trials-Conducted-Asia_20151101_Biospectrum_Article.pdf
28. Bigger may not be better for China's "super hospitals", July 2015, Reuters <http://www.reuters.com/article/china-health-hospitals-idUSL3N0ZH2I20150715>
29. More Arab patients seek treatment in Korea hospitals, May 2015, The National UAE <http://www.thenational.ae/uae/health/more-arab-patients-seek-treatment-in-korea-hospitals>
30. The Right place for clinical trials in Asia, Start with Korea, Konect, June 2016 http://kcc.konect.or.kr/jsp/popup/file/Start%20with%20Korea_20160609.pdf
31. SCI-Consortium and Novotech case study 3
32. The Korean Society of Medical Informatics, Healthc Inform Res. 2014 Jul; Going Abroad of Korean Health Information Systems <http://synapse.koreamed.org/DOIx.php?id=10.4258/hir.2014.20.3.161>
33. Smart hospitals continue to evolve, September 2014, The Korea Herald <http://www.koreaherald.com/view.php?ud=20140928000178>
34. Electronic Health Records in China Provide Opportunities for International Healthcare Ventures, January 2016 <http://paccentury.com/electronic-health-records-in-china/>
35. HKMA's Three-Pronged Approach to Drive eHR Adoption and Sharing among Doctors, ehealth http://www.ehealth.gov.hk/en/publicity_promotion/ehealth_news_09/hkma_three_pronged_approach.html
36. The International Property Rights Index 2016, <http://internationalpropertyrightsindex.org/countries>. Published 2016, Accessed August 23, 2016
37. Xinhua Insight: Better IP protection promises bigger fortune for China-U.S. firms, Sept 2015, New China http://news.xinhuanet.com/english/2015-09/27/c_134664714.htm
38. Novotech Case Study 4
39. Regulatory Environment and Clinical Trials in South East Asia, Ellick Wong <http://www2.cde.org.tw/Data/CDEDoc/Documents/Regulatory%20Enviroment%20and%20Clinical%20Trials%20in%20South%20East%20Asia.pdf>

- 40. U Sahoo, Clinical Research in Asia: Opportunities and Challenges, 2012
- 41. Conducting Clinical Trials in Asia, Jun 2006 <http://www.appliedclinicaltrialsonline.com/conducting-clinical-trials-asia-0?id=&pageID=1&sk=&date=>
- 42. 10 monster traffic jams from around the world, October 2012, BBC
<http://www.bbc.com/news/magazine-19716687>
- 43. Report on the protection and enforcement of intellectual property rights in third countries, July 2015, European Commission <https://euipo.europa.eu/ohimportal/documents/11370/0/>
- 44. Global Clinical Trials in Asia: Challenges and Opportunities, May 2010 http://www.diaglobal.org/productfiles/22993/day%203/402/s402%2001_vijay%20prabhakar.pdf

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