The Evolution of Clinical Research in East Asia

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Clinical research has become increasingly globalized and a large patient pool of nearly 1.6 billion people exists in East Asia, which is approximately 22% of the world’s population.¹ Trial activity has steadily increased in Asia Pacific overall with pockets of growth in various East Asian countries.²,³ The biggest relative change between 2006 and 2012 of newly registered clinical trials was also observed in East Asia.⁴ But how has clinical research evolved in this region? This analysis aims to identify the answer to that question by leveraging Trialtrove® and Trialpredict® data.

² Karlberg JPE. Clinical Trial Magnifier, 2011;4(1):7-23
⁴ http://www.appliedclinicaltrialsonline.com/decline-clinical-trials-central-and-eastern-europe-fluctuation-or-trend
Dataset and definitions

The dataset was exported on 11 February 2015 and included trials meeting the following inclusion criteria:

- Phase I to III
- Industry linked
  - Industry sponsor(s) included as primary sponsor or collaborator
- Trial location includes China, Hong Kong, Japan, South Korea (Korea), and/or Taiwan\(^5\)
- Trial has been initiated or is planned
  - Initiated trials include the following trial statuses:
    - Ongoing (Recruitment is open, closed, or temporarily closed)
    - Completed (Trial completion and/or full results of primary endpoints are reported)
    - Terminated (Limited to trials terminated after recruitment started\(^6\))

Trials in the dataset were classified by geographic breadth into the following categories:

- Local: Trial is limited to a single East Asian location
- Multinational: Trial takes place in multiple locations
- Global: Trial includes 2 or more continents
- Asia: Trial includes an East Asian location(s) and at least one other location in Asia
- East Asia: Trial is limited to any combination of the five East Asian locations

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\(^5\) For the purpose of this analysis, Taiwan and Hong Kong were considered separately from China since all have distinct health regulatory agencies and individual trial registries. Also, while the UN sub-region of East Asia is defined as China, Japan, North and South Korea, Mongolia, and Taiwan, Mongolia and North Korea were excluded due to limited clinical trial activity.

\(^6\) Initiated studies do not include trials that were terminated while still in planning phases.
Results

Initiated clinical activity in East Asia has increased dramatically from 2002-2012 and appears as if it will continue to rise.\(^7\) 5,977 studies initiated over the 10 year period; 220 trials reportedly began in 2002 and trial numbers grew until 890 started in 2012. The number of initiated local trials rose from 141 to 538 and local studies consistently comprised the majority each year. In contrast, 79 and 352 multinational trials started in 2002 and 2012 respectively. (Figure 1)

![Figure 1. Initiated Trials in East Asia (2002–2012)](image)

To determine where clinical research has taken place and where it is moving to, trials were compared by location and status by calculating the percentage of trials per location by trial status.\(^8\) The largest percentage of completed trials by far included Japan, followed by Korea. Approximately half of completed studies took place in Japan while almost 30% were in Korea. The same is true for terminated trials, but with a smaller difference in percentage between Japan and Korea. When reviewing trends for ongoing and planned studies, proportions per status shift a bit. Although Japan still leads for ongoing studies, the percentage decreases in comparison to completed and terminated trials and further decreases for Japan's planned activity. On the other hand, clinical activity for Korea ramped up for ongoing trials (44%) and the location becomes a close second to Japan. The percentage of ongoing trials also increases for China and continues to rise when considering planned activity. Korea and China lead in the percentage of planned trials with 39% and 36%, respectively. Overall, it appears that the proportion of clinical research in East Asia may be shifting from Japan and toward China and Korea based on the percentage of trials per status. (Figure 2)

\(^7\) The temporal view of trial activity is limited to the 10 year period of 2002-2012 to account for varying trial age of disease coverage in Trialtrove® and reporting bias as there is typically a delay in public disclosure of trial conduct. Also, trial activity may be reported without a specified start date.

\(^8\) Since multinational trials include multiple East Asian locations, the total percentage for each trial status will not add up to 100%.
Overview of initiated trials: What’s the past and current state of research?

The initial temporal analysis found more local than multinational trials had started recruitment between 2002 and 2012. This is also the case for the entire set of initiated trials ($n = 9,198$) and 65% take place in a single East Asian location. Multinational studies were primarily global and 90% involved two or more continents. The minority either took place only in East Asia or other regions in Asia. As such, the remainder of the analysis defines geographic breadth as either local or multinational, with multinational encompassing Global, Asia, and East Asia. (Figure 3)
A country-specific analysis reveals Japan’s clear lead, the majority of which were local trials. Approximately half of initiated activity included Japan as a location. Korea was the second most active location and mostly consisted of multinational trials. The different locations have historically strongly favored either multinational or local trials, except for China. While China initiated more local studies, only 55% were local. In contrast, local trials comprised 78% of Japan’s initiated studies. The remaining three locations favored multinational studies, particularly Hong Kong (Multinational: 94%). (Figure 4)

The percentage of initiated trials per country for each year was calculated to elucidate any temporal trends in geographic distribution and potential migration of initiated trials. Japan was consistently involved in the highest percentage of trials, however, the percentage for Korea increased at a faster pace each year and the location became a closer second place to Japan over time. Annually, Japan was involved in 32-49% of initiated trials and averaged 44%. In 2002, Korea participated in 17% of initiated trials and the percentage to 41% in 2012. The overall average was 23%, but if trial activity is limited to the more recent 5 year time period of 2007 to 2012, Korea averaged participation in 37% of initiated studies. (Figure 5)

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9 Percentage of initiated trials per location was calculated by dividing the number of trials initiated in that location and year by the total number of trials initiated in that year. Again, the time period is limited to the 10 year span of 2002-2012.
China’s inclusion as a location increased slightly and stabilized to just below 25% of initiated trials per year. Taiwan was also fairly consistent and averaged 21%. Hong Kong’s percentage of trial activity decreased over time, although a slight uptick was observed in 2012. (Figure 5)

Figure 5. Geographic Distribution of Initiated Trials Per Start Year (2002–2012)

Across all initiated trials, both Japan and China conducted more local studies while the remaining three locations were involved in more multinational ones. To determine whether this preference has evolved, a temporal analysis of geographic breadth preference for each location was done. In general, preferences did become more apparent over time for all locations but China. China did not appear to have a clear preference as they oscillated between initiating more local or more multinational studies over the decade. There was a slight trend toward local studies since China’s overall trial count for the decade included 29 more local trials. (Figure 6)

10 Rather than individually plotting the counts of local and multinational trials for each of the five locations, the preference is demonstrated by subtracting the number of local studies from the number of multinational trials.
Japan clearly favored local trials and eventually settled at starting approximately 150 more local studies yearly. The other locations initiated increasingly more multinational trials, but both Hong Kong and Korea lessened the gap in recent years. Although an uptick in multinational trials in 2012 is seen for nearly all locations, this could potentially be due to delayed reporting of local trials with a 2012 start date. (Figure 6)

![Figure 6. Geographic Breadth Preference by Location (2002–2012)](source)

With regard to general characteristics of initiated trials, Phase III was most common and comprised nearly half of initiated trials. Sponsorship is fairly diverse since 617 industry sponsors initiated an average of 16 trials each. (data not shown) Novartis was the most common industry sponsor and Pfizer was a close second. Trials were included if a company served as the primary sponsor or a collaborator; as such, trial counts are not limited to studies where sponsors acted as the primary sponsor. However, collaboration was not a common occurrence and a single sponsor conducted 77% of initiated trials. It is likely that Novartis did act as the primary sponsor in most, if not all, of these trials. Both top sponsors only initiated 6% of the 9,198 trials. (Table 1) This relatively low proportion of activity from the larger pharmaceutical companies can likely be attributed to the numerous East Asian companies sponsoring trials in the area. The most active local sponsors are all headquartered in Japan with Otsuka (308 trials), Takeda (248 trials), and Astellas (241 trials) at the top. (data not shown)

11 Phase hybrids were grouped in the later Phase of investigation. The category of Phase III includes Phase II/III trials and Phase II includes Phase I/II.
12 Sponsor trial counts include studies conducted by previously acquired companies. For instance, Chiron trials would fall under the trial counts for Novartis.
13 Local sponsors are defined as companies whose headquarters are based in one of the five East Asian locations.
Table 1. Characteristics of Initiated Trials in East Asia

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th># TRIALS</th>
<th>% TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2160</td>
<td>23%</td>
</tr>
<tr>
<td>II (includes I/II)</td>
<td>2869</td>
<td>31%</td>
</tr>
<tr>
<td>III (includes II/III)</td>
<td>4169</td>
<td>45%</td>
</tr>
<tr>
<td>Top 5 sponsors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>578</td>
<td>6%</td>
</tr>
<tr>
<td>Roche</td>
<td>492</td>
<td>5%</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>481</td>
<td>5%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>392</td>
<td>4%</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>364</td>
<td>4%</td>
</tr>
<tr>
<td>Collaboration</td>
<td>2142</td>
<td>23%</td>
</tr>
<tr>
<td>Single Sponsor</td>
<td>7056</td>
<td>77%</td>
</tr>
</tbody>
</table>

*Sponsor may be primary sponsor of trial or a collaborator. Trial counts include studies conducted by previously acquired companies.

Source: Citeline’s Trialtrove®, February 2015

The top therapeutic area measured by trial count was Oncology. Oncology trials were the most prevalent not only overall but also for each individual phase. Metabolic/Endocrinology (Metabolic) trials were second overall and for Phase I and III trials while Autoimmune/Inflammation (AI) was the second most common for Phase II. For all therapeutic areas but oncology, Phase III trials comprised approximately half of each area’s initiated clinical research. On the other hand, nearly half of Oncology’s initiated activity consisted of Phase II trials. (Figure 7)
Although Oncology was the largest therapeutic area, the most common indication overall was Type 2 Diabetes. In fact, only 2 of the top 5 diseases were cancers: specifically Non-Small Cell Lung (NSCLC) and Breast. The remaining indications were the Cardiovascular (CV) and AI indications of Hypertension and Rheumatoid Arthritis. In line with trends observed for therapeutic areas, all of the non-oncology indications were most commonly Phase III trials while Phase II trials led in trial numbers for both cancers. (Figure 8)

Figure 8. Top 5 Indications in Initiated Trials by Phase

<table>
<thead>
<tr>
<th>Rank</th>
<th>Indication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Type 2 Diabetes</td>
<td></td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>Non-Small Cell Lung Cancer</td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hypertension</td>
<td>50</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>4</td>
<td>Breast Cancer</td>
<td>50</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rheumatoid Arthritis</td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Source: Citeline’s Trialtrove®, February 2015

Overview of planned trials: What’s in store for the near future?

320 planned trials were disclosed in the public domain as of 11 February 2015. This number may seem small, however, the dataset is limited to planned trials that explicitly named one of the 5 East Asian locations. There are likely other trials planned for the region that have not yet disclosed exact locations in the public domain.

More local trials than multinational ones are currently planned and the proportion of local trials increased to 76% of planned studies from 65% of initiated research. Phase I has the largest percentage of planned trial activity (38%) and the vast majority are local (112 local vs 9 multinational). This contrasts with the fact that Phase I was least prevalent among initiated studies; however, Phase III is nearly as represented, comprising 35% of planned activity. The sponsor with the largest number of planned studies is Takeda, followed by Novartis. Notably, Novartis is the only company that was also a top 5 sponsor for initiated studies. Again, single sponsor studies are more common by far at 80% of planned activity, which is close to the 77% reported for initiated trials. (Table 2)
Table 2. Characteristics of Planned Trials in East Asia

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th># TRIALS</th>
<th>% TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic breadth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>244</td>
<td>76%</td>
</tr>
<tr>
<td>Multinational</td>
<td>76</td>
<td>24%</td>
</tr>
<tr>
<td>Trial phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>121</td>
<td>38%</td>
</tr>
<tr>
<td>II (includes I/II)</td>
<td>87</td>
<td>27%</td>
</tr>
<tr>
<td>III (includes II/III)</td>
<td>112</td>
<td>35%</td>
</tr>
<tr>
<td>Top 5 sponsors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takeda</td>
<td>23</td>
<td>7%</td>
</tr>
<tr>
<td>Novartis</td>
<td>11</td>
<td>3%</td>
</tr>
<tr>
<td>Chong Kun Dang</td>
<td>8</td>
<td>3%</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>8</td>
<td>3%</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>8</td>
<td>3%</td>
</tr>
<tr>
<td>Collaboration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collaboration</td>
<td>63</td>
<td>20%</td>
</tr>
<tr>
<td>Single Sponsor</td>
<td>257</td>
<td>80%</td>
</tr>
</tbody>
</table>

*Sponsor may be primary sponsor of trial or a collaborator. Trial counts include studies conducted by previously acquired companies.

Source: Citeline’s Trialtrove®, February 2015

As previously stated, Japan no longer leads when it comes to planned trial activity. Korea is the most common location and is followed by China. The vast majority of Korea’s planned trials are local, which differs from the higher prevalence of multinational trials among Korea’s initiated research. China’s planned activity is also mostly local and consistent with the slightly higher number of local initiated studies for China. However, China’s proportion of local trials increased from 55% of initiated studies to 72% of planned ones. No change is observed for Japan and Taiwan with regard to geographic breadth preference in their planned studies. The number of planned trials for Hong Kong is limited, but the majority are multinational and in line with Hong Kong’s initiated research. (Figure 9)

Figure 9. Planned Trials by Location and Geographic Breadth

Source: Citeline’s Trialtrove®, February 2015
Among the planned trials divulged at the time of the data pull, the top therapeutic area is Oncology again, but not across all Phases. AI has the largest number of planned Phase III trials while Oncology leads for Phase I, II, and overall. CV is the second most common area, overall and for Phases I and III. AI is second for Phase II trials, which was also the case for initiated research. Planned studies have slightly more diverse trial phases than initiated trials, where Phase III was most common across all non-oncology areas. CV, Infectious Disease (ID), and Metabolic all have Phase I as the largest proportion of their planned trials, which fits with the large number of upcoming Phase I trials. The remaining therapeutic areas follow the same trends as initiated trials: Oncology primarily consists of Phase II and Phase III is most common for the rest. (Figure 10)

The top 5 indications for planned trials are nearly the same as for initiated trials; however, Rheumatoid Arthritis has been replaced by Dyslipidemia and Unspecified Solid Tumor. Both Dyslipidemia and Unspecified Solid Tumor were among the top 10 indications evaluated in initiated trials and Rheumatoid Arthritis just missed inclusion in the top 5 planned diseases by a single trial (data not shown). As such, the top indications remain consistent between initiated and planned trials but the rankings shifted. Also, 6 indications are listed in the top 5 due to ties between Type 2 Diabetes and Dyslipidemia (16 trials each) as well as Breast cancer (Breast) and Unspecified Solid Tumor (14 trials each). Four indications mostly have Phase I studies and includes the Oncology indication of Unspecified Solid Tumor. The other 2 Oncology indications of NSCLC and Breast primarily have Phase II activity planned. (Figure 11)
Enrollment trends analysis of completed trials: What can the past tell us about the future?

The enrollment trends analysis leveraged Trialpredict® data from completed trials with actual timing milestones reported in the public domain. All calculations are averages, and include:

- **Trial rate:** Average number of participants enrolled per month per trial (pt/mon)
- **Average reported number of sites per trial.**
- **Site rate:** Average number of participants enrolled per month per site per trial (pt/mon/site)

A total of 3,374 completed trials disclosed timing milestones in the public domain and enrolled an average of 45.5 pt/mon. An average of 54.1 sites were reported per trial, which results in a site rate of 0.8 pt/mon/site. (data not shown) Specific variables considered in this analysis were trial phase, therapeutic area, top indications in planned trials, and locations.

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14 In order to be classified as actual timing data in Trialpredict®, dates of enrollment or study implementation must be disclosed in sources such as peer reviewed journal articles, conference abstracts, company press releases, and study result reports. Timelines provided are at the level of the entire trial and are not site specific.

15 The number of reported sites is defined by Trialtrove® as the total number of sites as referenced in trial publications or registries.

16 Enrollment rate calculations used actual accrual figures, not target accrual. Trial and site rates are calculated averages and are not trial or site specific enrollment rates disclosed in the public domain.
Phase III trials had the highest trial rate at 60.4 pt/mon. They also had the largest average site numbers per trial (80 sites), which likely aided the achievement of such a large trial rate. Phase I studies had the lowest trial rate but they exhibited the highest site rate. The average site rate for Phase I trials was 3.8 pt/mon/site and is much higher than both Phase II and III trials. (Figure 12) However, the faster rate per site is likely due to Phase I studies typically enrolling healthy volunteers rather than patients. Also, Phase I’s low trial rate is unlikely to cause lengthy recruitment periods since Phase I trials generally have much smaller targets for accrual. In fact, the average actual accrual for Phase I studies in this set was 38 pt while the average was 957 pt for Phase III. (data not shown)

Across the 8 therapeutic areas, CV had the highest trial rate and averaged 123.6 pt/mon. (Figure 13) CV trials also had the largest average accrual with 1780 pt. In comparison, the average accrual for the other areas ranged from 289 to 639 pt. (data not shown) As such, a high trial rate was necessary to enroll the large number of subjects within a reasonable time frame, which could be attributed to the fact that CV trials averaged the highest reported number of sites (107.9 sites). (Figure 13)

The lowest trial rates were observed in CNS and Oncology (20 and 24.4 pt/mon, respectively). Both had the lowest site rates as well with Oncology rounding out the bottom. Oncology trials reported the second highest number of sites, speaking to potential difficulties in recruiting cancer patients since high sites numbers generally results in more aggressive trial rates. The highest site rate goes to ID, which also had the second highest trial rate. (Figure 13)
As CV had the highest trial rate, it is not surprising that the highest trial rates among the top indications in planned trials were achieved by the two CV indications. Dyslipidemia trials had the top trial rate (119.4 pt/mon), followed by Hypertension at nearly half the rate (56.9 pt/mon). Expectedly, the Oncology indications had the lowest trial rates. The limited number of Unspecified Solid Tumor trials that provided actual timing milestones averaged a trial rate of 11.3 pt/mon. This was the lowest trial rate and is less than 10% of Dyslipidemia’s trial rate. (Figure 14)

Both Breast and NSCLC enrolled approximately 36 pt/mon. Although lower than the trial rate for other indications, these two trial rates are higher than the trial rate found across all Oncology trials. Breast studies used the highest number of sites (111.9 sites) and showed the lowest average site rate as a result (0.3 pt/mon/site). Dyslipidemia trials averaged the second largest number of sites, however, these trials had the highest site rate at 1.8 pt/mon/site. Given the large trial and site rates observed for Dyslipidemia trials, it appears that this indication should be relatively easy to recruit in East Asia. On the other hand, Breast trials will require a large number of sites in order to achieve moderate trial rates. (Figure 14)
The last characteristic considered for the enrollment trends analysis was trial site location, however, enrollment trends by location were split by geographic breadth in order to compare location specific rates and determine how trends could differ for local and multinational trials.

Local trials in China had the highest trial rate at 20.7 pt/mon, but Japan trailed closely at 18.7 pt/mon. Hong Kong had the lowest rate at 6.2 pt/mon but the number of local trials is limited. It appears that the few local trials in Hong Kong were mostly single center since the average number of sites was 1.1, which led to the highest site rate of 5.8 pt/mon/site. (Figure 15)

The largest number of sites were reported by Japanese studies (21.8 sites). Since local Japanese trials used a larger number of sites, these trials go from having the highest trial rate to the lowest site rate. All other locations enrolled between 2.9-5.8 pt/mon/site, but Japan only enrolled 0.9 pt/mon/site. (Figure 15)

On the whole a fairly low numbers of sites were used per local trial since the average number of sites used across all local studies was 15. This likely correlates with the fact that local studies had an average accrual of 189 participants overall. (data not shown) Considering the smaller average trial size, a large number of sites weren’t necessary.
Different trends emerge for multinational trials. China leads again but Korea is at the bottom instead of Hong Kong. Notably, the average number of subjects enrolled in a month seems to depend on the number of sites used for multinational trials since all locations had a site rate of 0.5 or 0.6 pt/mon/site. The fact that China had the highest trial rate appears to be associated with the fact that Chinese multinational trials used the highest number of sites on average. Likewise, Korea had the lowest number of sites and the lowest trial rate. As such, the exact East Asian location does not appear to affect enrollment trends for multinational trials. This is also suggested when comparing multinational and local trials for Hong Kong and Taiwan. Both locations exhibited the lowest trial rates when conducting local trials but competitive trial rates were observed for both locations. These high trial rates were likely aided by other locations and the number of sites involved in their multinational studies. (Figure 16)
Summary and conclusions

Clinical trial activity in East Asia has grown driven to a large extent by local studies conducted by a single sponsor. Japan leads in trial numbers overall, but the proportion of activity may be shifting to China and Korea. Except for China, all locations appear to have clear geographic breadth preferences, but Korea’s preference may be changing. Phase I activity appears to be increasing while Phase III research remains stable. Although the most common therapeutic area is consistently oncology, the top indications for initiated and planned trials are not limited to cancer.

In terms of what we can apply to the future, high trial rates demonstrated by Phase III studies seemingly require large site numbers and Phase I trials will likely experience high site rates. High enrollment rates in general are likely for CV and ID trials. Cancer trials on the other hand may have some difficulties in enrollment, especially for Breast. Lastly, it appears that the exact location may affect enrollment rates for local studies but not for multinational ones.

Significant changes aren’t observed but shifts in various characteristics and trends do exist. As such, research in East Asia is certainly growing but does not appear to be evolving dramatically.