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Geographical Distribution and Trends of Clinical Trial Recruitment Sites in Developing and Developed Countries

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Abstract: To improve clinical trial efficiency and enhance participant recruitment, many clinical trials open recruitment sites in multiple countries and regions. Understanding the geographic distribution of clinical trial recruitment locations is important for clinical trial planning and monitoring. In this study, we analyzed the geographic distribution and trend of clinical trial recruitment sites in developing and developed countries. The data was extracted from ClinicalTrials.gov, the largest public clinical trial registry that documents clinical trials from 190 countries and areas. To analyze the recruitment geographic distribution, we extracted 1,839,565 recruitment sites from 182,841 clinical trial summaries submitted to ClinicalTrials.gov. The recruitment site locations were normalized using geocoding techniques. The results show that the top five countries that host participant recruitment sites are the United States, Germany, France, Canada, and Japan. During this time, the United States is the major force of clinical trial recruitment, hosting nearly 50% of the clinical trial recruitment sites. The top five fastest-growing countries are China, Republic of Korea, Ukraine, the Russian Federation, and India. We categorized all documented countries into 14 regions. The results indicate that recruitment sites in Northern America, the European Union, and Asia accounts for 90.46% of the total recruitment sites. In terms of the growth rate of global recruitment site share, Asia has the highest average growth rate of site share at 28.37%. The global share for many developing regions also increase at a relatively fast speed, such as Central America at 19.60%, Western Africa at 18.40%, and the Middle East at 16.52%. Two regions showing a decline in the average global share are Northern America at -4.59% and the Caribbean at -6.62% yearly. Overall the results show that developed countries with strong pharmaceutical and medical research history continue to host a majority of clinical trial recruitment sites. Northern America, the European Union, and Asia host 90.46% of all clinical trial recruitment sites. Many developing regions, such as Central America, Africa, and the Middle East show fast growth rates.

Keywords: Geographic distribution of clinical trials; developing country clinical trials; recruitment location; clinical trial recruitment trends; clinical trials; data analysis of clinical trials

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1. INTRODUCTION

Globally, clinical trials have been growing rapidly [1]. The globalization of clinical trials is driven by the demand of new drug development [2, 3], international research collaboration [4, 5], expansion of participant recruitment [6-8], and economic incentives to reduce trial costs [9]. To improve transparency and patient recruitment, more and more clinical trials around the world release trial protocols and trial result data to the public domain, such as registering on ClinicalTrials.gov [10, 11]. Public access to clinical trial data not only increases the transparency of clinical trials, but also creates new opportunities to improve medical research. For example, several studies have explored the potential of using published clinical trial eligibility criteria to facilitate patient e-screening [12-14]. Some studies leverage the published trial data to examine clinical trial characteristics [15], discover adverse event patterns [16], and analyze research gaps [17].

In this study, we analyzed the geographical distribution and clinical trial recruitment trends in developing and developed countries. Analyzing the distribution of trials can reveal important trends of clinical studies. For example, an analysis of the WHO data [18] showed that clinical research was shifting from high-income countries to low- and middle-income countries. In another study that focused on cardiovascular clinical trials, researchers found that multi-regional trials noticably increased during 2001-2003 and during 2009-2012. This study also found that cardiovascular trials typically recruited more patients and involved more recruitment sites [19]. Thiers et al. discussed the global trend of industry-sponsored clinical trials [20], and Richter [21] studied the network of clinical research and analyzed research collaboration using studies that recruited participants in multiple countries. Hoekman et al. [22] used the publication results of 1,445 registered trials to study the leadership of clinical trials. Novak et al. [23] analyzed the trend of clinical trial recruitment in the Central and Eastern Europe regions. Their analysis showed a surprising decline of clinical trial in the area. Galsky et al. [24] studied the accessibility of recruitment sites for patients diagnosed with cancer in the United States. They found that many clinical trials recruitment sites have a long geographic distance for patients to visit, and the distance could be an important factor that drives participation rate down for cancer trials. Hsiehchen et al. [25] discussed multinational collaboration of clinical trials using data extracted from ClincialTrials.gov. The result of the study revealed that the growth of multinational collaboration on clinical trial has been stagnant, but clinical trials have become much bigger in scale.

In this study, using data obtained from ClinicalTrials.gov, we analyzed and discussed the geographical distribution of *recruitment sites* of clinical trials among developing and developed

countries. The countries were divided into fourteen regions, and we analyzed the trends of recruitment site setups among these regions. We focused on analyzing the distribution and trend of recruitment sites. A recruitment site is a facility that a clinical trial set up to enroll targeting population to participate in a clinical study. Some small trials could have only one recruitment site, whereas many trials set up recruitment sites in multiple locations to increase recruitment ability and reduce recruitment time. Planning and setting up recruitment sites is a crucial step for carrying out clinical trials [20, 26]. Understanding geographic patterns and trends of recruitment sites can benefit clinical trial investigators and policy makers in planning and monitoring clinical trials.

2. METHODS

2.1 Dataset Retrieval and Parsing

We obtained the clinical trial data from ClinicalTrials.gov [10, 11]. Each clinical trial record was stored in an XML format file. We developed a program to parse the XML to retrieve information about the recruitment locations. In total, we extracted 182,841 trials and 1,839,565 sites. To analyze the growth of recruitment sites across different years, we used the documented "first received date" as the timestamp for a trial; thus, the years of the trials range from 1999 to 2014 based on the "first received date" on ClinicalTrials.gov. Many trials started to report study protocols to ClinicalTrials.gov from 1999, therefore the year 1999 was selected as the starting time in this study. Many more recent trials (e.g. 2015, and 2016) are still adding or removing recruitment sites to enroll patients. Therefore, to use more stable data, the end of the study time span was selected at 2014. For some trials, the recruitment sites were removed from the record after the recruitment process was finished. BecauseClinicalTrials.gov consitantly tracks changes and updates made to the data records, and we were able to recover the removed sites. The recovered recruitment sites were added to the trial recruitment location list. In total, we recovered 329,960 sites in 15,395 clinical trials. The recovered sites were 17.95% of the total extracted 1,839,565 recruitment sites after site recovery. The extracted recruitment site addresses are not properly normalized and structured. To address this challenge, we developed a geographic encoding program that used the Bing Map API to assign standard geographic attitude and longitude to each of the recruitment location.

2.2 Country Region Categorization

To analyze the growth of different geographic regions, we categorized the 190 countries and areas that reported on ClinicalTrials.gov into 14 different regions according to the United Nations' country grouping. The regions include: Eastern Africa, Middle Africa, Northern Africa, Southern Africa, Western Africa, the Caribbean, Central America, South America, Northern America, Asia, Eastern Europe, European Union, Middle East, and Oceania. We then analyzed the growth rate of the global recruitment site share in each of the countries and regions.

2.3 Calculating Recruitment Site Share in a Global Context

To evaluate the global share of clinical trial recruitment sites across time in different countries and regions, we followed the same measurement method proposed in Thiers's work [20]. After all the recruitment sites were extracted, we calculated the total number of trials conducted in each country and region each year. The share of global recruitment sites for a given country or region can be calculated as the percentage of recruitment sites in the country among all recruitment sites during the time period:

$$\text{Site Share}_{[year]} = (\text{number of recruitment sites in the country})_{[year]} / (\text{total number recruitment sites})_{[year]} \quad (1)$$

Furthermore, the formula to calculate the yearly growth rate of global recruitment site share for a given country or region is defined as:

$$\text{Growth Rate of Global Share}_{[year]} = (\text{share}_{[year+1]} - \text{share}_{[year]}) / ((\text{share}_{[year+1]} + \text{share}_{[year]})/2) \quad (2)$$

Thus, the growth rate of global site share is calculated by dividing the share difference of two consecutive years (share[year+1] – share[year]) with the average share of the two years (share[year+1] + share[year])/2.

3. RESULTS

3.1 Summary of Documented Trials per Year

To provide a general background of trials on the ClincialTrial.gov [10, 11], Figure 1 shows the summary and trend of submitted trials each year. We can see from the figures that in general the amount of submitted trials increased over the years. Since 2005, the submitted trials increased significantly to more than 10,000 trials per year. The 2005 increase can be attributed to the new policy from the International Committee of Medical Journal Editors (ICMJE) that requires clinical trials to register on ClinicalTrials.gov for publication [27]. Currently, ClinialTrials.gov provides a brief summary of the geographic distribution of clinical trials that submitted to the registry. However, there still lacks a detailed study that analyzes the geographic distribution and trend of recruitment sites. Many clinical trials set up recruitment sites in multiple countries and regions. Understanding the geographic distribution of recruitment locations is important for trial planning and monitoring. In this study, we fill this research gap by analyzing the geographic distribution of clinical trial recruitment sites.

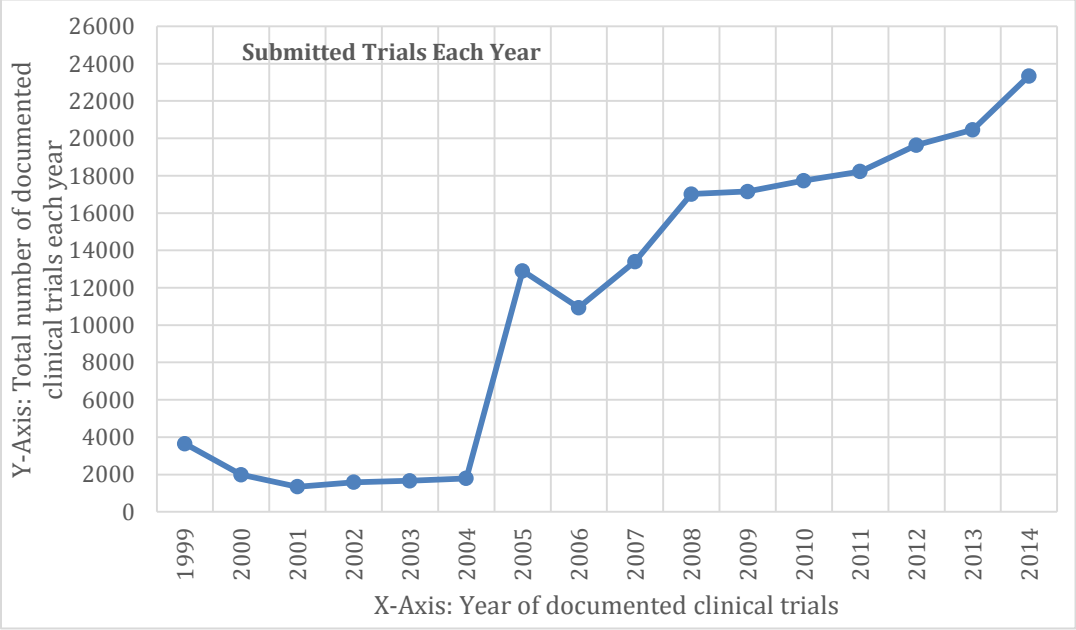
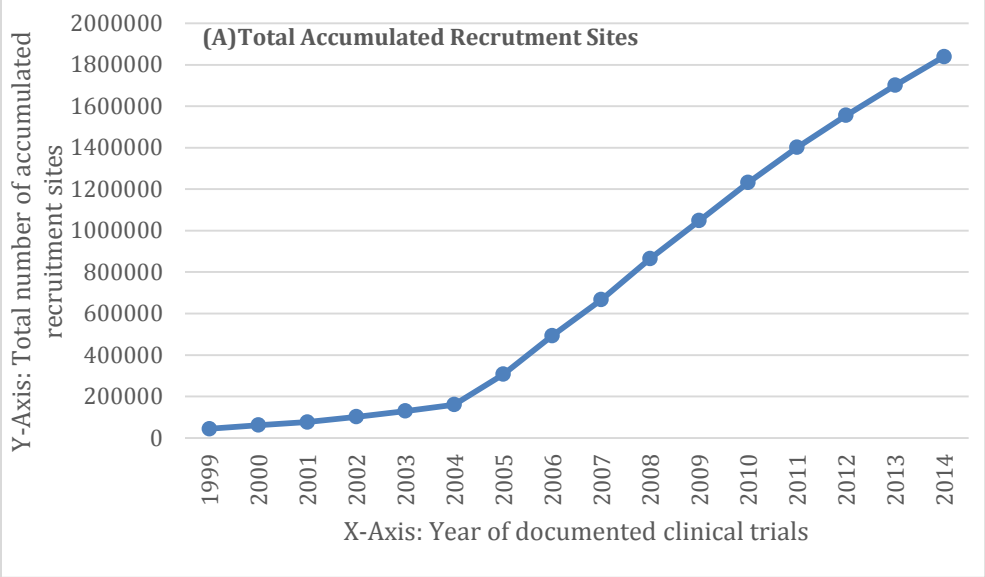


Figure 1: Submitted trials each year. The horizontal axis shows the years of the trial submission. The vertical axis shows the total trials of a year. The x-axis shows the year of trials. The y-axis shows the total number of clinical trials documented for the corresponding year.

3.2 Total Submitted Recruitment Sites

A clinical trial can enroll participants at multiple recruitment sites. Figure 2.A shows the total accumulated recruitment sites from 1999 to 2014 on ClinicalTrials.gov. At December 2014, there were 1,839,565 recruitment sites reported. On average, 114,973 recruitment sites were documented on the repository each year. The submitted recruitment sites also increased significantly since 2005. However, (See Figure 2.B) the yearly submitted recruitment sites peaked at 2008 at 198,527. Since then there has been a decline of documented recruitment locations each year, even though the submitted clinical trials continued to grow from 2009 to 2014. One possible reason is that many trials after 2008 are still at the planning and recruitment stage, because our timestamp for the trials is the "first received date". The recruitment site may not be fully documented.



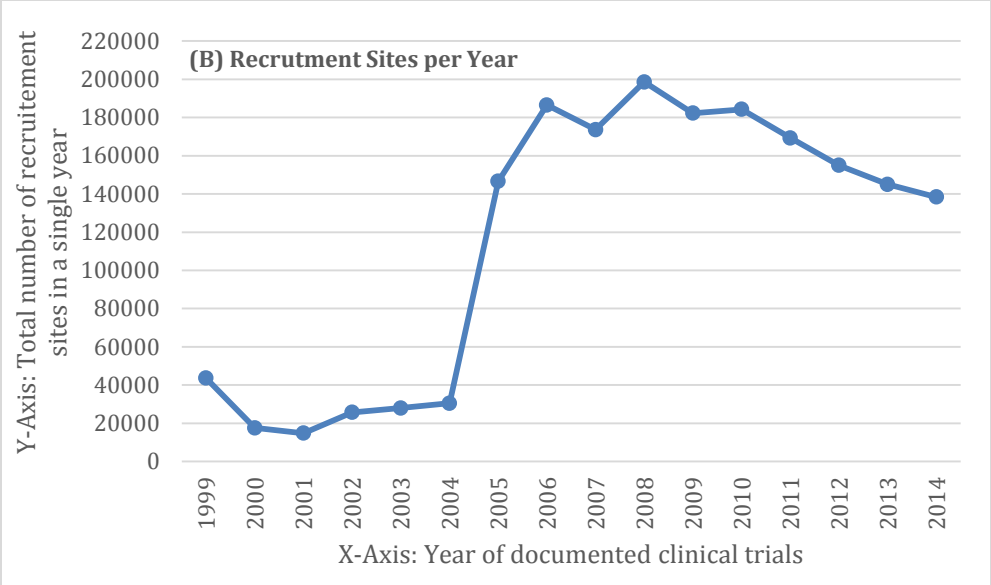


Figure 2: (A) Total accumulated recruitment sites. The x-axis shows the year of the trial documented. The y-axis show the total number of accumulated recruitment sites documented. (B) Documented recruitment sites per year. The x-axis show the year of the trial documented. The y- axis shows the total recruitment sites of a single year.

3.3 Intensity and Growth of Recruitment in Countries

Table 1 displays the top 25 recruitment-intensive countries by calculating the trial number, recruitment site number, total global site share (see Formula 1), average site share growth (see Formula 2), and average hosted sites per trial. The average hosted site per trial is calculated as the average number of recruitment sites in each trial (average hosted site = #sites / #trials) given a country. The growth of global site share describes the average annual growth rate among the global recruitment markets. In this work, we discovered that the top 25 countries hosted 91.51% of the recruitment sites. The top five countries in terms of total recruitment sites are the United States, Germany, France, Canada, and Japan. Most of the top countries are economically developed and have a strong medical research and development record.

Table 1: Top 25 Recruitment-Intensive Countries Hosted 91% of the Recruitment Sites

Country	# Trials	# Sites	% Total Site Share	% Average Share Growth	Hosted sites per trial
United States	90420	940264	49.40	-4.60	10.40
Germany	14076	115694	6.08	12.16	8.22
France	13679	100362	5.27	4.76	7.34
Canada	15079	63705	3.35	-4.20	4.22
Japan	4043	59106	3.11	17.92	14.62
United Kingdom	11582	49639	2.61	0.10	4.29
Italy	8502	48373	2.54	10.30	5.69
Spain	8137	47114	2.48	14.05	5.79
Russian Federation	3449	27599	1.45	25.91	8.00
Poland	4559	27512	1.45	17.49	6.03
China	6891	26612	1.40	36.19	3.86
Belgium	6566	24644	1.29	6.77	3.75
Australia	5218	24143	1.27	2.77	4.63
Korea, Republic of	6913	22633	1.19	32.16	3.27
Netherlands	6686	22012	1.16	1.77	3.29
Brazil	4960	17784	0.93	16.20	3.59
Czech Republic	3155	17009	0.89	22.49	5.39
Hungary	2911	15693	0.82	22.49	5.39
India	2949	15494	0.81	22.59	5.25
Israel	5591	13409	0.70	14.71	2.40
Sweden	4367	12885	0.68	13.50	2.95
Argentina	2210	12871	0.68	9.28	5.82
Denmark	5410	11378	0.60	10.52	2.10
Mexico	2708	11218	0.59	19.50	4.14
Ukraine	1427	11135	0.59	32.06	7.80
Median Value	5410	24143	1.27	14.05	5.25

In the United States between 1999 and 2014, the results demonstrated that there are 940,264 recruitment sites established for 90,420 trials. Recruitment sites in the U.S. alone accounted for 49.40% of all recruitment sites. Among the top five countries, Japan has the highest average hosted sites at 14.62 sites per trial, followed by the United States at 10.40 sites per trial, and Germany at 8.22 sites per trial. In terms of the growth rate of recruitment sites among global share, the top growing countries are China (36.19%), Republic of Korea (32.16%), Ukraine (32.06%), the Russian Federation (25.91%), India (22.59%), Czech Republic (22.49%) and Hungary (22.49%). The high growth rate of recruitment site shares indicates the fast development of clinical trial recruitments in Asia and Eastern Europe. Alternatively, the United States (-4.60%) and Canada (-4.20%) show a relative decline in recruitment

growth rate, although when counted in absolute site share, the United States still maintain a dominant status by the end of 2014.

3.4 Distribution of Recruitment in Global Geographical Regions

Table 2: Global Regions Recruitment Sites

Region	#Trial	#Sites	% Total Site Share	% Average Share Growth	Hosted Sites Per Trial
Northern America	98876	1003970	52.76	-4.58	10.15
European Union	53516	558403	29.35	8.01	10.43
Asia	25616	153389	8.06	28.37	5.99
Eastern Europe	11700	67902	3.57	13.92	5.80
South America	7231	41979	2.21	13.65	5.81
Oceania	5610	27927	1.47	3.30	4.98
Middle East	7022	16422	0.86	16.52	2.34
Central America	3025	12811	0.67	19.60	4.24
Southern Africa	2320	10518	0.55	9.26	4.53
The Caribbean	2018	3933	0.21	-6.62	1.95
Northern Africa	1229	2574	0.14	16.45	2.09
Eastern Africa	1157	1921	0.10	16.56	1.66
Western Africa	545	880	0.05	18.40	1.61
Middle Africa	145	222	0.01	15.85	1.53
Median Value	4317.5	14616.5	0.765	14.885	4.385

Table 2 shows the distribution of recruitment sites among 14 geographical regions. The results indicates that Northern America, the European Union, and Asia host more than 90.17% of the recruitment sites globally during 1999-2014. There was a significant increase of recruitment sites in Asia, with an average increase of global share at 28.37% per year, which is the fastest-growing region. However, the average sites per trial in Asia was 5.88 sites which still lag behind Northern America at 10.15 sites per trial and the European Union at 10.43 sites per trial. This result indicates that Asia has a potential to enhance the ability of setting up more recruitment sites, given the dense population in the region and its fast research development in medical domain. Note that when comparing the average sites per trial, the European Union (EU) as a single region shows a higher value of sites per trial than individual countries within the EU. For example, the EU as a whole hosts 10.43 sites per trial, while the top country Germany host 8.22 sites per trial and the second country France host 7.34 sites per trial. This result indicates that many EU trials actually tend to established more recruitment sites in multiple countries. For example, if:

- Trial1 recruited in [Germany, France]
- Trial2 recruited in [Germany]
- Trial3 recruited in [France]

Then, Germany has 2 trials 2 sites and the average recruitment site per trial is 2/2=1. Similarly, France has 2 trials 2 sites and the average recruitment site per trial is 2/2=1. In total, Germany and France together have 3 trials 4 sites and have 4/3=1.33 average recruitment sites per trial, which is larger than Germany or France alone. The result also implies that clinical trials in EU are more collaborative in terms of international clinical trial recruitment.

3.5 Regional Share Trends

Figure 3 shows the change of global share of trial recruitment sites for the 14 regions from 1999 to 2014. The total share for Northern America decreased from 89.9% in 1999 to 45.6% in 2014. The share for the United States is relatively stable since 2009 with a smaller decline. The share for the European Union increased from 14.7% in 2004 to 32.6% in 2014, and its average growth is 8.20%; the share of EU also seems to have been stable since 2009. At the same time, the share for Asia increases from 1.7% in 2004 to 11.0% in 2014. Asia is the fastest-growing area. In many developing countries and areas, such as Asia, Central America, and Western Africa, there is a consistent fast growth rate in trial recruitment; however, they still have a smaller share of the global recruitment sites.

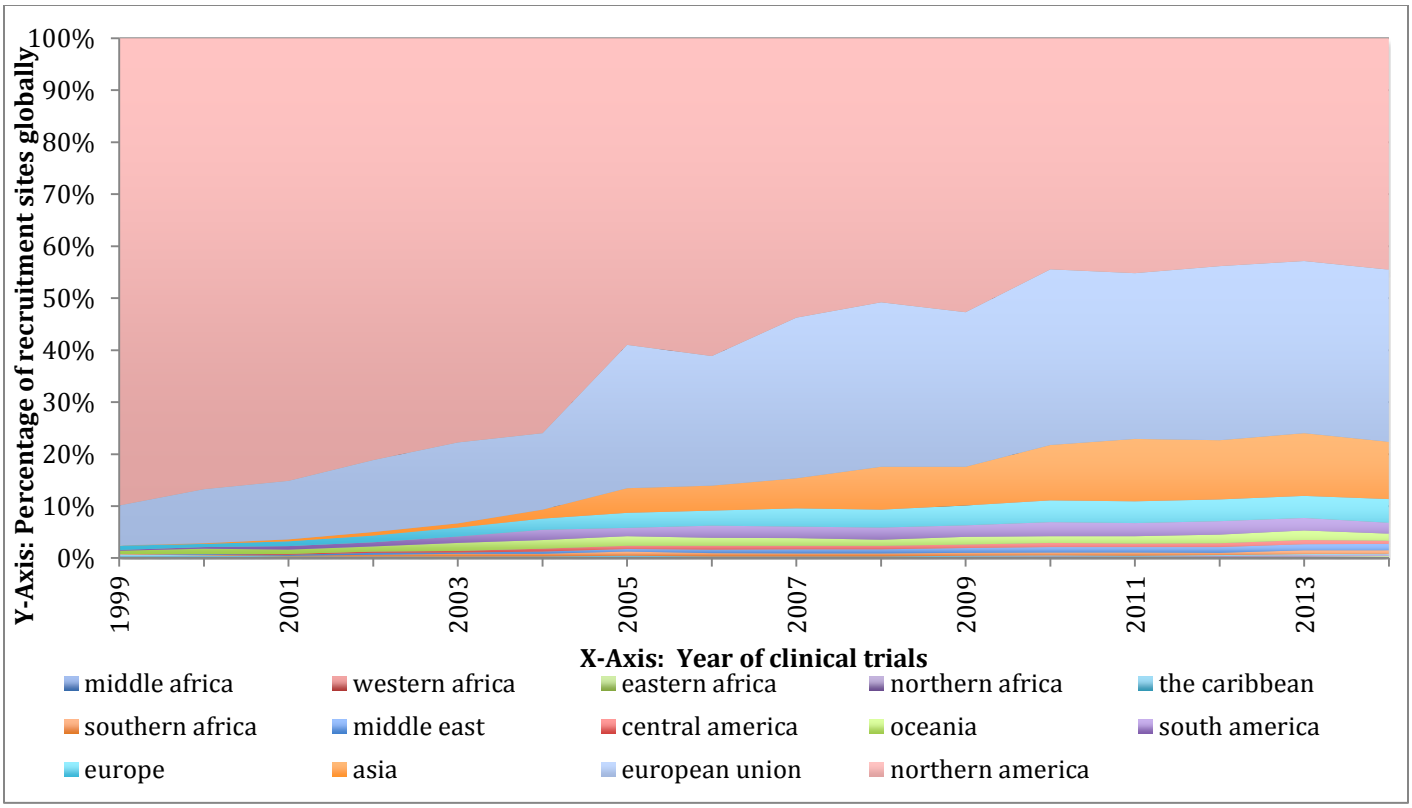


Figure 3: Yearly global share of recruitment sites. The y-axis shows years documented clinical trials from 1999 to 2014. The y-axis shows the percentage of recruitment sites globally in each of the region. A color band represents a region.

3. 6 Discussion

In this study, we collected 182,841 clinical trials and 1,839,565 recruitment sites from ClinicalTrials.gov. We observed a sturdy rise of documented clinical trials globally during 1999-2014. In 2014, there is close to 24,000 trials submitted to ClinicalTrials.gov. The reported clinical trial recruitment sites also increased with the growth of clinical trials. However, yearly reported recruitment sites reached a peak of approximately 200,000 sites in 2009.

United States is still the strongest force of clinical trial recruitment during 1999-2014. However, U.S. has a declining trend (-4.60% yearly growth rate) in the global share of setting up recruitment sites. Canada is another major country that shows similar declining trend (-4.20%). Therefore, the total global share of recruitment sites for Northern America drops -4.58% yearly on an average during 1999-2014. This could be attributed to several factors. A recent analysis [28] reported that the investment of medical research in U.S. has increased at 0.8% in the recent years, whereas globally the investment increased at a faster rate. Another study [29] suggested that NIH-funded trials decreased 9% from 2006 to 2014, but the study also observed a rise of clinical trials sponsored by industry in U.S. The decline of United

States' share of recruitment sites could also be linked to the faster growth of international trial recruitments among developing countries [20, 30, 31]. Many U.S. led trials have been trying to recruit more participants in the developing countries [1, 30, 32]. Mexico, by contrast, is a Northern American country that showed quick growth of recruitment sites share at a rate of 19.50%. The other area that we can see a decline in terms of the global share of recruitment sites is Caribbean (-6.62% yearly growth rate).

European Union remains a strong region for clinical trial recruitment. EU hosts approximately 29% of the total clinical trial recruitment sites during 2009-2014. However, based on the ClincialTrial.gov data, EU's global share of recruitment sites has a relatively small growth during the time. Globally speaking, EU region is one of the low growth areas (0 %< growth rate<10%). The low growth areas include EU (8.01% yearly growth), Oceania (3.30%), and Southern Africa (9.26%). However, countries within EU demonstrated different growth rates. Developed EU countries showed relatively low growth rates, such as France (4.8%), United Kingdom (0.10%), and Netherland (1.77%), whereas some eastern and central EU countries showed a faster growth rates among global share, such as Hungary (22.49%), Czech Republic (22.49%), and Poland (17.49%). A few Eastern Europe countries also demonstrated fast growth, such as Ukraine (32.06%) and Russian Federation (25.91%). As we discussed in the result section, another characteristics of clinical trials in EU is that they are more collaborative internationally, therefore on an average the EU trials host more recruitment sites per trial. From 2001, EU developed the Clinical Trial Directive (CTD) policy to support consistent clinical trial procedure across EU countries. However, a few studies [33-36] demonstrated that the CTD has negative impacts on clinical research in the EU, including the decline of non-commercial clinical trials in some EU countries [33], particularly in UK, Netherland, and France [35]. This could be one of the factors that associated to a slow growth of recruitment among several developed EU countries. Since 2014, EU regulators have been promoting a new Clinical Trial Regulation (CTR) policy [37] to replace CTD. CTR includes an innovative central portal and a coordinated review system, which could facilitate future clinical trial research in EU. Another factor that associated with the low growth of recruitment sites in EU is similar to U.S. that many pharmaceutical companies outsource recruitment sites to the developing countries [20, 30, 31].

Asia is the fastest growing region for clinical trial recruitment. The growth rate of global recruitment site share for Asian is 28.37% during 1999-2014. On the county level, India (22.59% yearly growth rate) has been a popular country for international clinical trial recruitment, though there are ethical concerns of clinical trial recruitments in India [31, 38-41]. In response to the concerns, policy

and law authorities in India announced laws and guidelines [42] to tighten the regulation of clinical trials in India. These new policies could increase the transparency and compliance of the clinical trials. However, some analysis suggested that the new policies may reduce the number of trial sites because only registered institutional ethics committees can approve trial protocols [43, 44]. China is another country that attracts international clinical trials. During 2009-2014, China has the highest growth rate of recruitment site share at 36.19% per year. There are also ethical concerns of clinical trials conducted in China [41, 45, 46]. In Asian, the global recruitment site shares of two developed countries, Republic of Korea (32.16%) and Japan (17.92%), also grow relatively fast, which are rare among developed countries. Despite the fast growth in Asian countries, the total share of recruitment sites and hosted sites per trial are still relatively low, except Japan hosts about 3% of all global recruitment sites and hosts 14.62 sites per trial. Therefore, based on the trend of the fast growth and relatively low starting point, we are likely to see more growth in trial recruitment in Asian countries in the near future. Oceania region hosts 1.47% of all recruitment sites and the region shows a growth rate of 3.30% and hosts 4.98 sites per trial. Australia is the only Oceanian country on the top 25 recruitment-intensive countries. Australia has a low average growth rate of global share at 2.77% yearly. Australia hosts 4.63 sites per trials.

In South America, Mexico has a fast growth rate at 19.50% per year in global recruitment site share. Argentina has a lower growth rate at 9.28%, but the absolute global share of recruitment sites of Argentina is 0.68%, which is higher than Mexico's at 0.59%. Argentina also hosts more sites (5.82 sites) per trial than Mexico (4.14). The South American region as a whole hosts 2.21% of all recruitment sites and has a growth rate of global share at 13.65%.

Most other developing regions, including Middle East, Central America, and Africa regions have a relatively fast speed of growth rate in the global share of recruitment sites. However, the absolute share of recruitment sites is still very low (<1%) for each of these regions.

4. CONCLUSION

This study analyzed the growth and distribution of clinical trial recruitment sites among developing and developed countries. The results show that developed countries with strong pharmaceutical and medical research history are still leading in setting up clinical trial recruitment sites at the time of this study. The top five countries for establishing trial recruitment sites were the United States, Germany, France, Canada, and Japan. The United States hosted close to 50% of the clinical trial recruitment sites from 1999-2014. However, the global share of Northern America declined from 89.9%

in 1999 to 45.5% in 2014, while the global share for Asia increased from 1.7% in 2004 to 11.0% in 2014. Overall, Northern America, the European Union, and Asia hosted 90.46% of all clinical trial recruitment sites; whereas many developing regions, such as Central America, Africa, and the Middle East demonstrated a faster growth rates.

5. ACKNOWLEDGEMENT

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