

Industry Trials in BRIC Countries – Russia, Moscow and St. Petersburg Stand Out

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Summary

The four BRIC countries (Brazil, Russia, India and China) represent 60% of the world's population but contribute as little as 5.9% of active industry sponsored clinical trial sites globally.

The industry seemingly prefers to only locate large phase III trials to the BRIC countries for the most popular diseases under clinical testing.

These four BRIC countries hold enormous potential to become major players in the international clinical research arena.

A clear exception is China, with potential hindered by a strict and conservative regulatory framework and shortage of experienced, accredited investigators/sites.

Abstract

The four so-called "BRIC" countries -- Brazil (191 million), Russia (142 million), India (1,136 million) and China (1,331 million) -- together account for 59.7% of the world population. Yet they account for only 5.9% of industry sponsored clinical trial sites globally -- and only 22.2% of among emerging countries. However, a recent 4.3% drift has been noted from North America and Europe to emerging countries, with about a third of those 6,500 sites located to BRIC. This study compares industry sponsored clinical trial activities among the four countries. Russia has more phase II-IV trials (n=620) than any of the other three BRIC countries. Brazil and India both account for about 75% of Russia's total. China has fewer than 50% (n=268). The proportion of locally conducted trials -- i.e. those conducted in one single country -- is highest for China (49.3%), followed by Brazil (17.6%), India (9.3%) and Russia (5.3%). The number of active sites for multi-national industry sponsored trials is highest for Russia (n=3,364), followed by India (n=2,149), Brazil (n=1,988) and China (1,044). The number of sites per active multi-national trial is highest for China (9.4 sites per trial), followed by Russia (8.4), India (7.3 and Brazil (6.9). The vast majority of multi-national trials are phase III -- about 85% for China and 75% for the other three BRIC countries. Oncology (27.2%) and cardiovascular (24.4%) account for more than 50% of multi-national trials in the four BRIC countries. Some sponsors are highly active in those countries, with over 700 active sites in total. Others are less active, with fewer than 400 active sites. Sites in Russia and China are both mostly located (56-57%) in two major cities -- namely Moscow (31.2%) and St. Petersburg (24.9%) in Russia, and Beijing (34.3%) and Shanghai (22.4%) in China. On the other hand, India has a more diversified geographic distribution of sites, with only 20.5% in the two most active cities of Bangalore and Mumbai. Clearly, the four BRIC countries hold enormous potential to become major players in international clinical research. A continuing drift of study sites from North America and Europe to emerging countries is anticipated, especially to the BRIC countries. A clear exception is China, due to its strict and conservative regulatory framework and shortage of experienced, accredited investigators/sites undermining its opportunity to significantly expand in the international clinical research playing field.

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Introduction

The four so-called "BRIC" countries – Brazil (191 million), Russia (142 million), India (1,136 million) and China (1,331 million) – together account for 59.7% of the world's population (Figure 1) have over the past year strongly improved their relative growth in the industry sponsored clinical trials arena.¹ They are expected to become stronger economic, political, scientific and technological global players in the future. REF Up to now, however, they only account for around 5.9% of industry trial sites globally. Even among emerging countries, their share is only 22.2% (Figures 2–3).²

However, a 4.3% drift has lately been noted in trial sites from North America and Europe to emerging countries – with about a third of those 6,500 sites located to the four BRIC countries (0.5% to Russia and India each for instance).¹ Russia is developing extremely well among emerging trial regions, followed by India and Brazil. China is not achieving its obvious potential as the world's most populous country.

The launch of the ICH GCP Guideline in 1996 opened the door for globalization of industry sponsored clinical trials,³ introducing Good Clinical Practice (GCP) as an international ethical and scientific quality standard for designing, conducting, recording and reporting trials involving human subjects. Compliance with this standard anywhere in the world provides assurance that the rights, safety and well-being of trial subjects are protected and that clinical trial data are credible. Its impact has been significant. By adopting the principles of the ICH GCP guideline, pharmaceutical companies can now collect trial data worldwide, rather than only in established regions, for filing new drug applications in established regions.

The main reason for the rapid globalization of clinical research is that emerging countries can offer large patient populations for testing new medicinal products. The industry turned to new regions partly due to difficulties recruiting sufficient patients in North America and Europe.

Countries with large populations such as the four BRIC countries are obviously more attractive than smaller countries because they can offer more study sites per protocol, making project management and study monitoring more efficient and cost effective. It can therefore be confidently predicted that BRIC countries will continue to be the main focus for the international pharmaceutical, biotech and medical device industry. A continuing drift of trials sites from established regions to those countries is anticipated.

Study objective

This study compares industry clinical trial activities among the four BRIC countries – by means of trial phase, number of trials and sites, number of sites per protocol, proportion of local and multi-national trials, therapeutic area and disease focus, sponsors' preferences and most active cities.

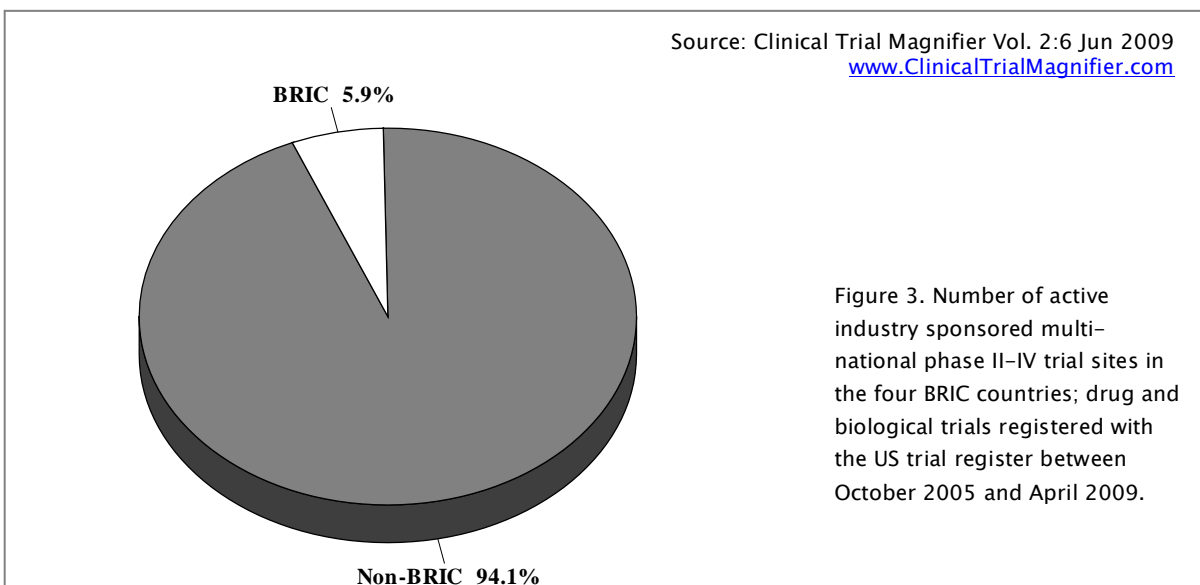
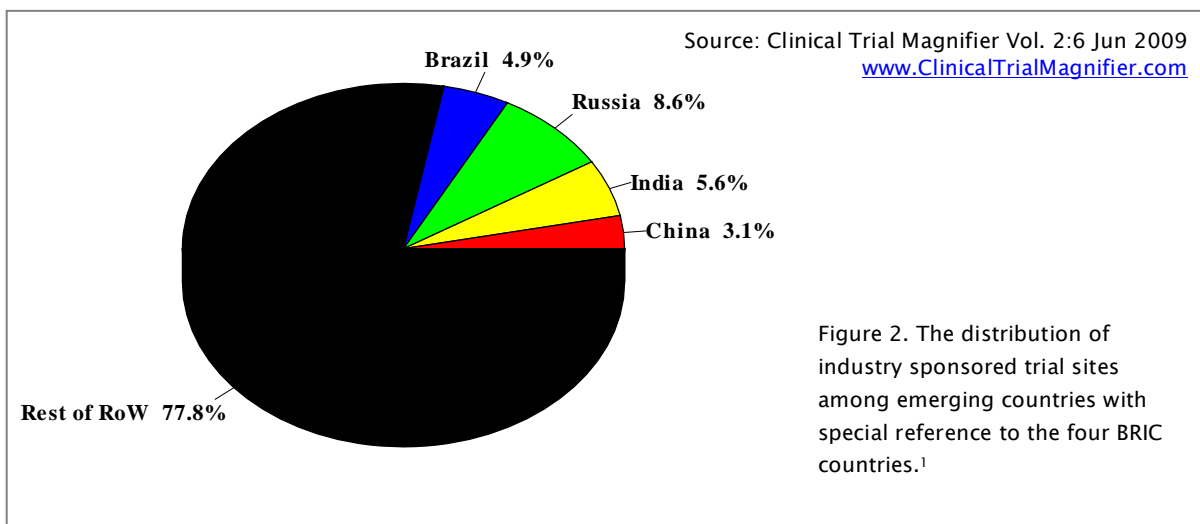
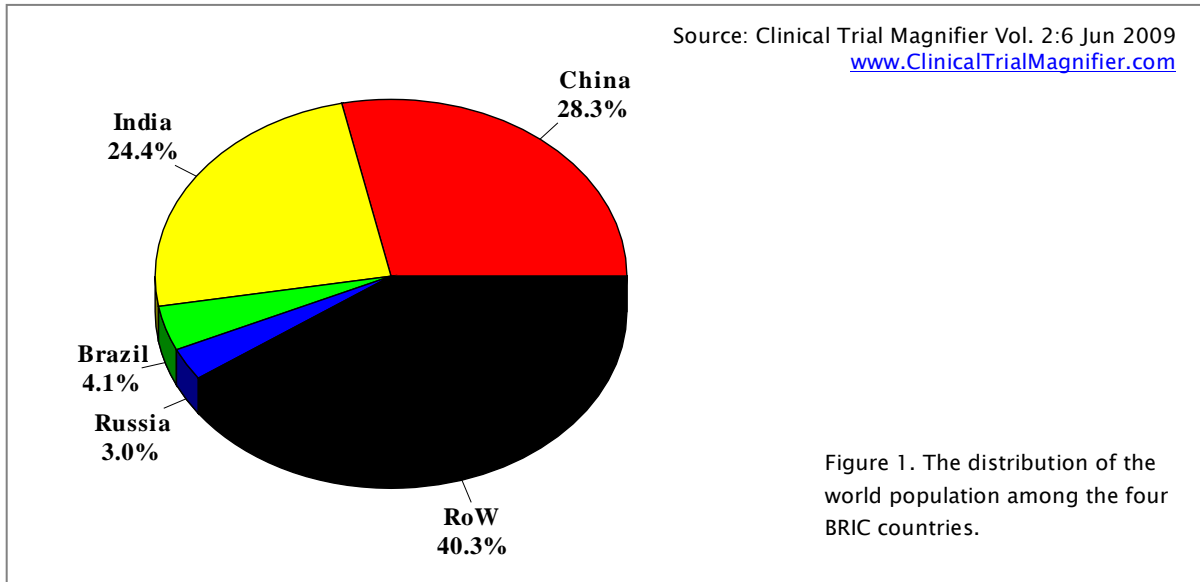
Material and Methods

All clinical trials registered with www.ClinicalTrials.gov were downloaded on April 29, 2009.⁴ Essential information was extracted and coded by a tailor-made SAS programme (Statistical Analysis System) developed by the author.⁵ The dataset was subsequently analysed using SAS.

Extracted information: Register identifier, date of first registration, date of study onset, date of last update, study phase (phase I–IV), type of study (observational or experimental), primary sponsor, therapeutic/disease area, study site location (i.e. country and city, with institution occasionally listed), global sample size, study status, and type of intervention being investigated.

Analysis Dataset: The following inclusion/exclusion criteria restricted the analysis: (I) Interventional studies of drugs and biologics were included, and not observational studies or clinical trials of devices, procedures or preventions; (II) Only phase II–IV defined trials; (III) Trials first registered between October 1, 2005 and April 29, 2009 were included, giving 43 months of data; (IV) Trials initiated on October 1, 2005 or later were included; (V) Only trials actively "recruiting" or following subjects ("ongoing") were included, and not trials under planning, completed, terminated or halted.

Phase I Trials: The Food and Drug Administration Amendments Act of 2007 came into law on September 27, 2007 and the law was enacted on September 30, 2007.⁶ The 2007 FDA Amendments Act expanded the requirement to register virtually all clinical trials involving drugs, biologics and devices. The registry data bank must include all "applicable" drug clinical trials as a condition of NDA approval. "Applicable" drug clinical trials include all controlled clinical investigations of a product other than "phase I" clinical investigations. For each drug under clinical testing there is on average some 20 phase I trials (unpublished observation based on the GlaxoSmithKline clinical trial data register) and the proportion of phase I trials in the US trial register is far below expected. For those reasons we have omitted phase I trials from the analysis.



Results

Number of trials and sites

The total number of industry sponsored phase II–IV drug and biological trials in the four BRIC countries are indicated in Tables 1–2 and Figures 4–9. They were registered with the US trial register and initiated between October 2005 and April, 2009, accounting for a total of 43 months of register data.

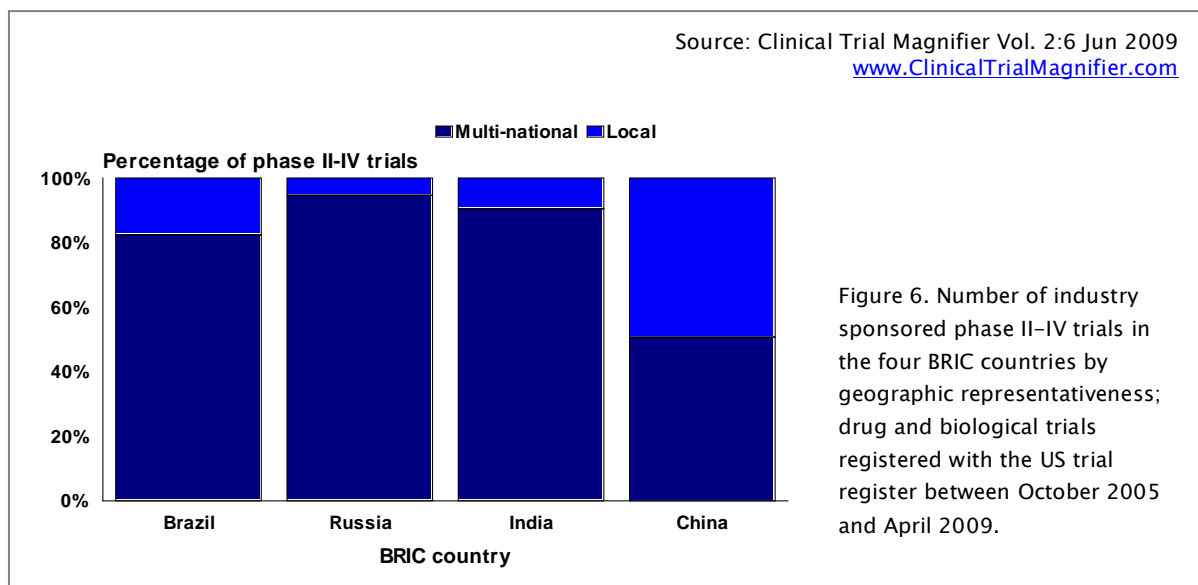
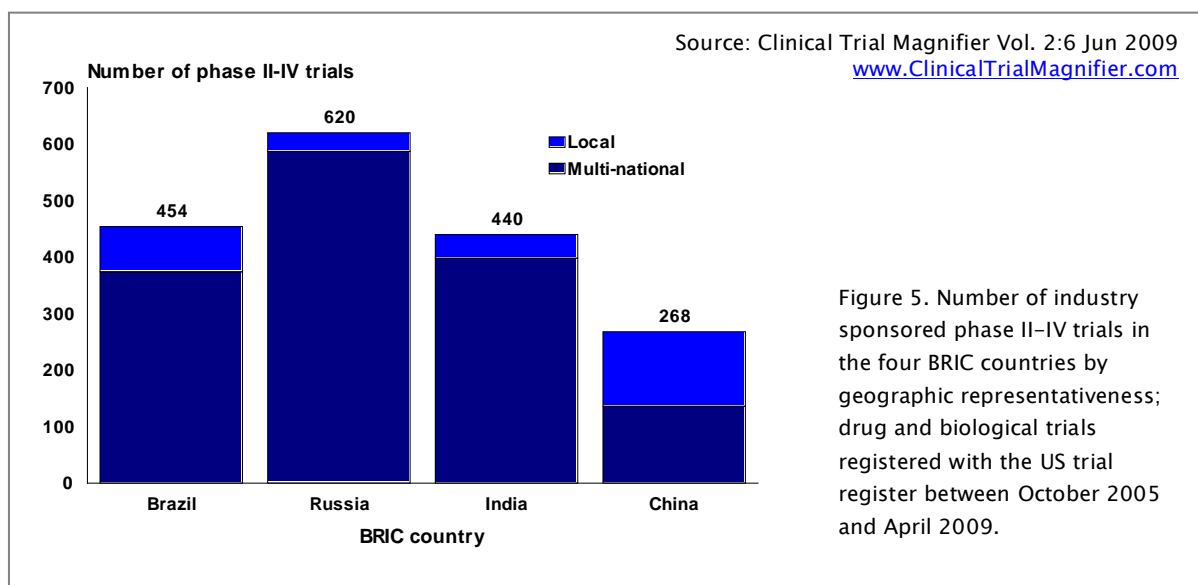
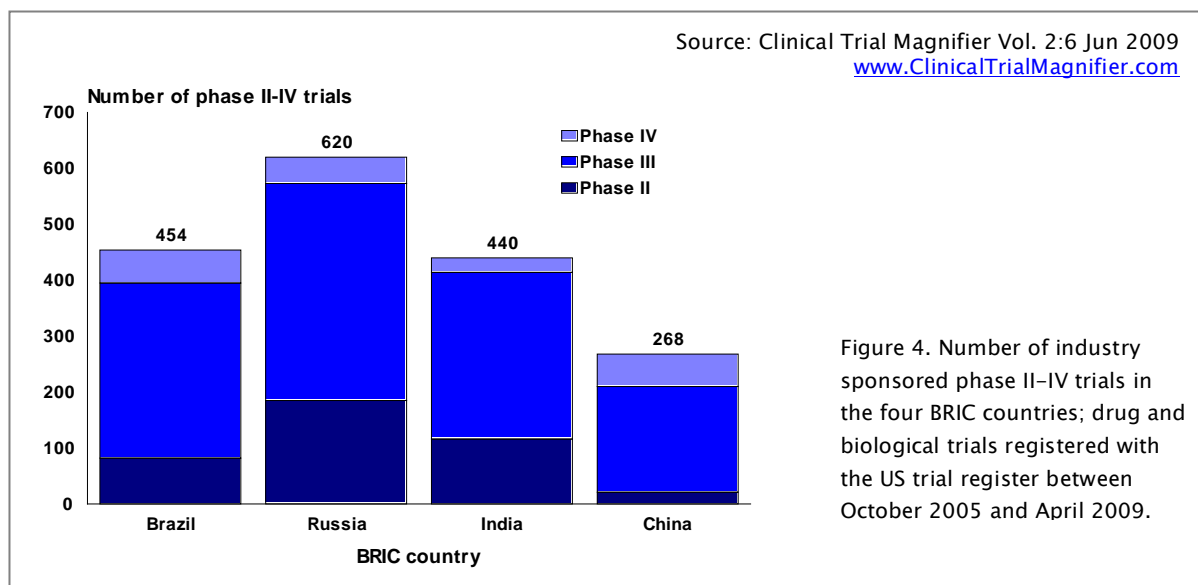
Russia accounts for more phase II–IV trials (n=620) than any of the other three BRIC countries. Brazil and India both have about 75% of the number of trials identified for Russia. China has fewer than 50% (n=268), (Table 1, Figure 4). The proportion of locally conducted trials – i.e. those conducted in one single country – is highest for China (49.3%), followed by Brazil (17.6%), India (9.3%) and Russia (5.3%), (Table 1, Figures 5–6). China is involved in only a third of the number of multi-national trials located in Russia; 136 compared to 587.

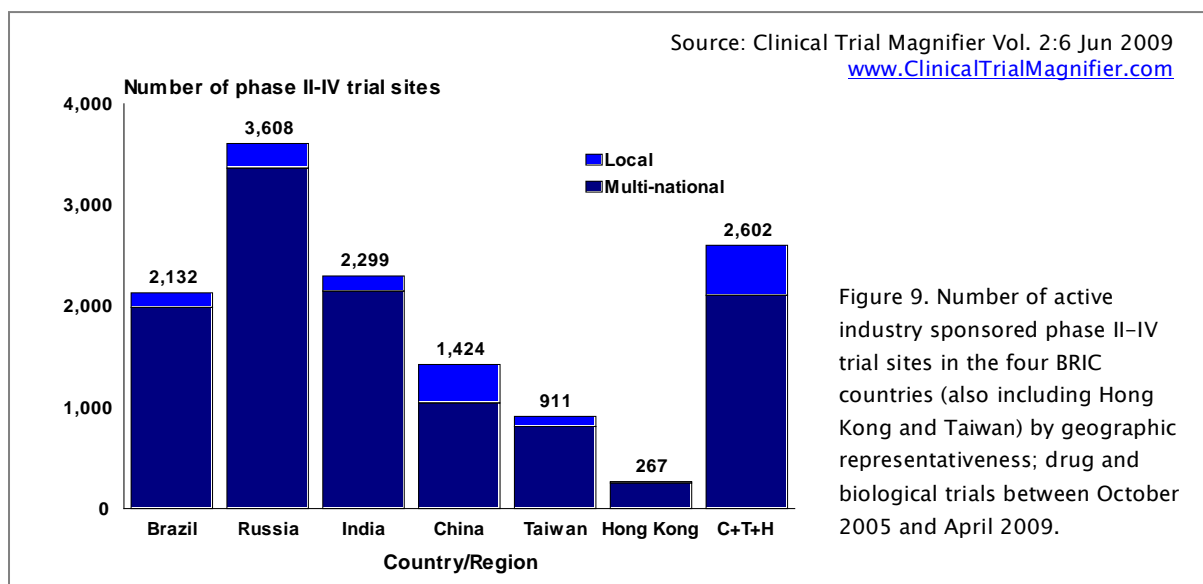
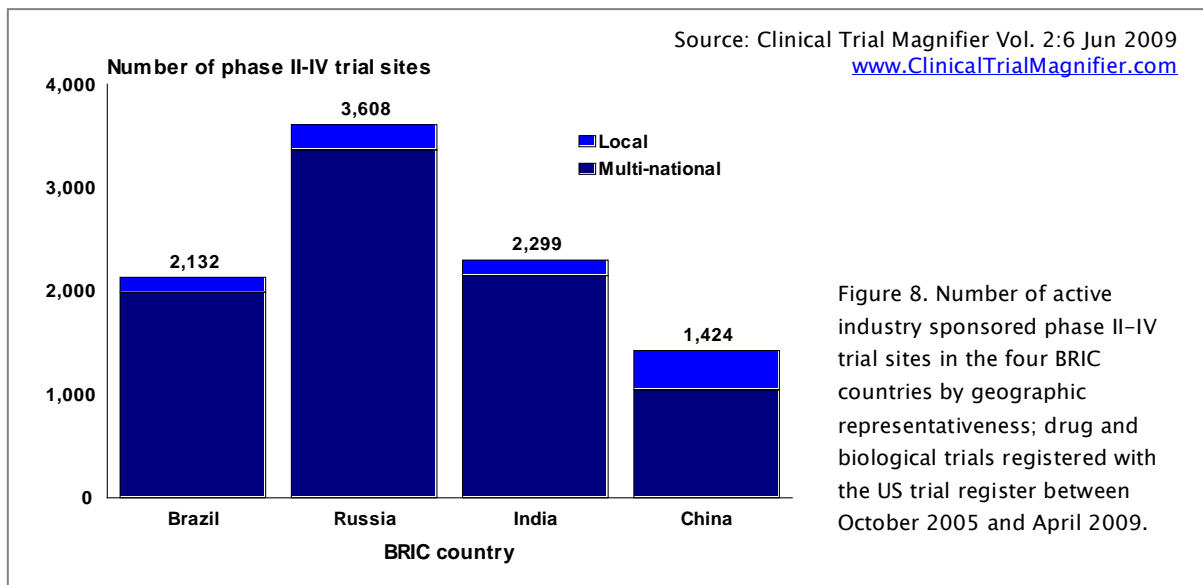
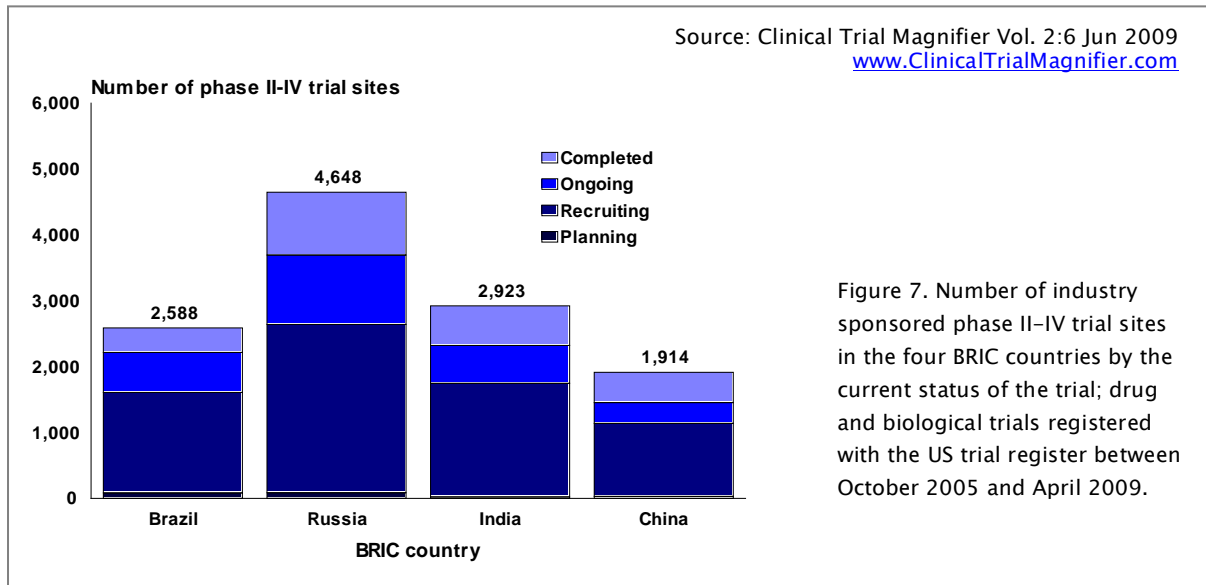
Table 1. Number of industry sponsored phase II–IV trials on drug and biologicals registered with the US trial register between October 2005 and April 2009 (43 months) for each of the four BRIC countries by trial phase and status; planning (Plan.), recruiting (Recr.), ongoing (Ong.) and completed (Compl.).

	Trial Phase	Local trials				Multi-national trials				Total				Grand Total
		Plan. n	Recr. n	Ong. n	Compl. n	Plan. n	Recr. n	Ong. n	Compl. n	Plan. n	Recr. n	Ong. n	Compl. n	
Brazil	II	3	2	1	3	3	35	20	15	6	37	21	18	82
Brazil	III	6	4	2	40	13	144	54	50	19	148	56	90	313
Brazil	IV	1	9	1	8	0	21	13	6	1	30	14	14	59
	Total	10	15	4	51	16	200	87	71	26	215	91	122	454
China	II	0	3	2	3	0	6	5	2	0	9	7	5	21
China	III	2	31	5	43	1	64	24	19	3	95	29	62	189
China	IV	4	22	4	13	0	9	3	3	4	31	7	16	58
	Total	6	56	11	59	1	79	32	24	7	135	43	83	268
India	II	0	8	4	5	1	50	23	25	1	58	27	30	116
India	III	2	2	5	9	2	161	50	67	4	163	55	76	298
India	IV	0	5	2	0	1	9	3	6	1	14	5	6	26
	Total	2	15	11	14	4	220	76	98	6	235	87	112	440
Russia	II	0	6	4	5	7	68	28	67	7	74	32	72	185
Russia	III	0	4	1	2	8	211	74	88	8	215	75	90	388
Russia	IV	0	4	2	5	2	12	6	16	2	16	8	21	47
	Total	0	14	7	12	17	291	108	171	17	305	115	183	620

Table 2. Number of active – recruiting or ongoing – industry sponsored phase II–IV trials and related sites on drug and biologicals registered with the US trial register between October 2005 and April 2009 (43 months) for each of the four BRIC countries by trial phase and geographic representativeness.

Recruiting/Ongoing	Trial Phase	Local		Multi-national		Total		Local	Multi	Total	Trials	Sites
		Trials n	Sites n	Trials n	Sites n	Trials n	Sites n	Sites per Trial %	Sites per Trial %	Sites per Trial %	Local of Total %	Local of Total %
Brazil	II	3	10	55	223	58	233	3.3	4.1	4.0	5.2	4.3
Brazil	III	6	91	198	1,512	204	1,603	15.2	7.6	7.9	2.9	5.7
Brazil	IV	10	43	34	253	44	296	4.3	7.4	6.7	22.7	14.5
	Total	19	144	287	1,988	306	2,132	7.6	6.9	7.0	6.2	6.8
China	II	5	36	11	48	16	84	7.2	4.4	5.3	31.3	42.9
China	III	36	215	88	886	124	1,101	6.0	10.1	8.9	29.0	19.5
China	IV	26	129	12	110	38	239	5.0	9.2	6.3	68.4	54.0
	Total	67	380	111	1,044	178	1,424	5.7	9.4	8.0	37.6	26.7
India	II	12	56	73	462	85	518	4.7	6.3	6.1	14.1	10.8
India	III	7	39	211	1,632	218	1,671	5.6	7.7	7.7	3.2	2.3
India	IV	7	55	12	55	19	110	7.9	4.6	5.8	36.8	50.0
	Total	26	150	296	2,149	322	2,299	5.8	7.3	7.1	8.1	6.5
Russia	II	10	72	96	626	106	698	7.2	6.5	6.6	9.4	10.3
Russia	III	5	45	285	2,507	290	2,552	9.0	8.8	8.8	1.7	1.8
Russia	IV	6	127	18	231	24	358	21.2	12.8	14.9	25.0	35.5
	Total	21	244	399	3,364	420	3,608	11.6	8.4	8.6	5.0	6.8





The trial status information for each of the four BRIC countries – planning, recruiting, ongoing or completed – is in Table 1 and Figure 7. The number of active trial sites – recruiting and ongoing – accounts for 74–82% of all sites for the four (Figure 7). The number of active phase II–IV trial sites by geographic distribution is in Table 2 and Figure 8. The number of active sites for multi-national trials is highest for Russia (n=3,364), followed by India (n=2,149), Brazil (n=1,988) and China (1,044). China has the largest

proportion of local trials and sites (Table 2).

The number of sites per active multi-national trial is highest for China (9.4 sites per trials), followed by Russia (8.4), India (7.3) and Brazil (6.9), (Table 2). The vast majority of multi-national trials are phase III – about 85% in China and 75% for the other three BRIC countries (Table 2).

Table 3. Number of active – recruiting or ongoing – multi-national industry sponsored phase II–IV trial sites on drug and biologicals registered with the US trial register between October 2005 and April 2009 (43 months) for each of the four BRIC countries by therapeutic area.

Therapeutic Area	Multi-national Recruiting/ongoing Sites				Total n	Percentage				Total %
	Brazil Sites n	Russia Sites n	India Sites n	China Sites n		Brazil Sites %	Russia Sites %	India Sites %	China Sites %	
Oncology	532	957	520	315	2,324	26.8	28.4	24.2	30.2	27.2
Cardiovascular	490	772	446	381	2,089	24.6	22.9	20.8	36.5	24.4
Endocrinology	162	376	344	63	945	8.1	11.2	16.0	6.0	11.1
CNS	111	372	249	45	777	5.6	11.1	11.6	4.3	9.1
Infectious	135	189	110	35	469	6.8	5.6	5.1	3.4	5.5
Respiratory	65	173	123	76	437	3.3	5.1	5.7	7.3	5.1
Rheumatology	222	86	67	21	396	11.2	2.6	3.1	2.0	4.6
GI & Hepatology	47	78	96	0	221	2.4	2.3	4.5	0.0	2.6
Kidney/Urology	34	115	57	6	212	1.7	3.4	2.7	0.6	2.5
Haematology	30	42	20	3	95	1.5	1.2	0.9	0.3	1.1
Orthopaedics	21	25	12	5	63	1.1	0.7	0.6	0.5	0.7
Allergy	25	24	9	3	61	1.3	0.7	0.4	0.3	0.7
O & G	4	6	1	29	40	0.2	0.2	0.0	2.8	0.5
Anaesthesiology&ICU	32	6	0	0	38	1.6	0.2	0.0	0.0	0.4
Ophthalmology	8	2	24	0	34	0.4	0.1	1.1	0.0	0.4
Dermatology	3	0	3	0	6	0.2	0.0	0.1	0.0	0.1
Surgery	0	0	2	0	2	0.0	0.0	0.1	0.0	0.0
Other	67	141	66	62	336	3.5	4.2	3.0	5.9	3.9
Total	1,988	3,364	2,149	1,044	8,545	100.0	100.0	100.0	100.0	100.0

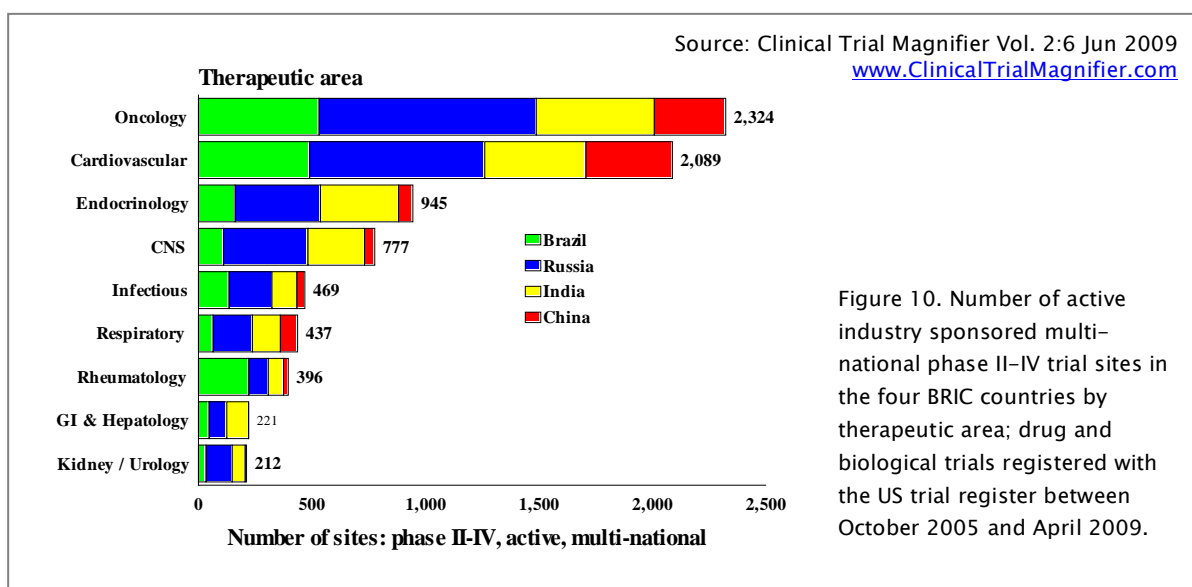


Figure 10. Number of active industry sponsored multi-national phase II–IV trial sites in the four BRIC countries by therapeutic area; drug and biological trials registered with the US trial register between October 2005 and April 2009.

Three regions with predominantly Chinese populations – PR China, Taiwan and Hong Kong – together account for 2,602 active local or multi-national sites, involving phase II-IV trials; 1,424, 911 and 267 sites, respectively (Table 2, Figure 9). This is slightly more than the corresponding numbers for Brazil and India.

Therapeutic area / diseases of active multi-national trials

Active oncology (27.2%) and cardiovascular (24.4%) multi-national trials together account for more than 50% of sites in the four BRIC countries (Table 3, Figure 10). Oncology and cardiology trials are somewhat

more prevalent in China, endocrinology in India, CNS in Russia and India, and rheumatology in Brazil (Table 3, Figures 11-13).

There are also notable differences in distribution of the 20 most popular diseases under trial in the four BRIC countries (Table 4, Figures 14-17). For instance, heart disease, venous disease and stroke are all more common in China, diabetes more popular in India, and arthritis relatively more frequent in Brazil.

Most active sponsors

Table 5 and Figures 18-19 details the 20 most active sponsors in the four BRIC countries. Some are highly

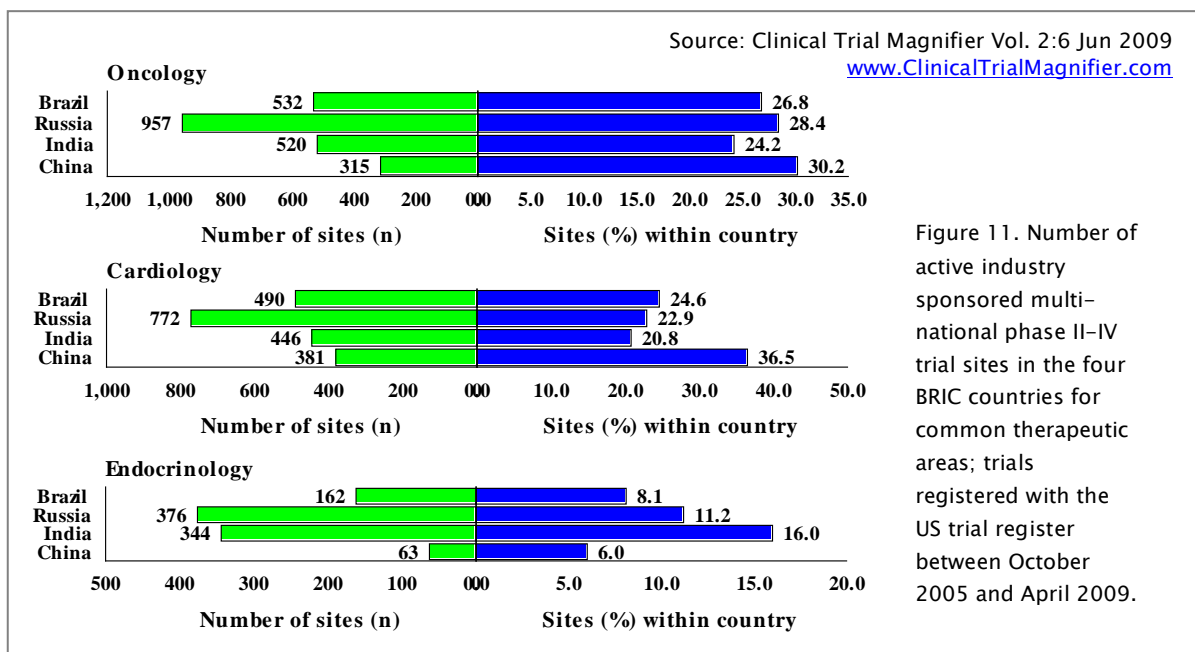


Figure 11. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for common therapeutic areas; trials registered with the US trial register between October 2005 and April 2009.

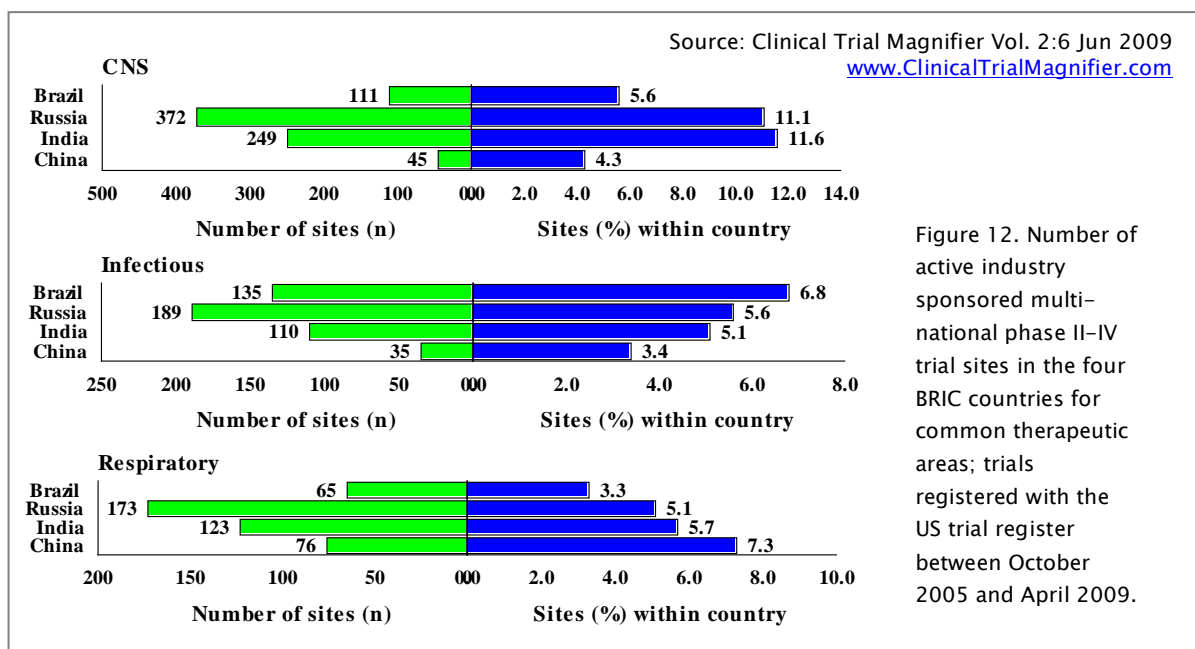


Figure 12. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for common therapeutic areas; trials registered with the US trial register between October 2005 and April 2009.

active with over 700 active sites. Others are less active with fewer than 400 active sites. Between the four countries, there are also differences in the relative level of activity of the most active sponsors. For instance, Hoffmann-La Roche has only 10 active sites in India, from a total of 827 in the four BRIC countries. Bayer locates close to 50% of their BRIC country sites in China alone.

Most active cities

Russia and China locate 56–57% of all their sites in two major cities, namely Moscow (31.2%) and St. Petersburg (24.9%) in Russia, and Beijing (34.3%) and Shanghai (22.4%) in China, (Table 6, Figure 20). On the other hand, India has a more diverse geographic distribution of sites, with only 20.5% in the two most active cities of Bangalore and Mumbai. Note that in India, sites from the top seven cities need to be tallied

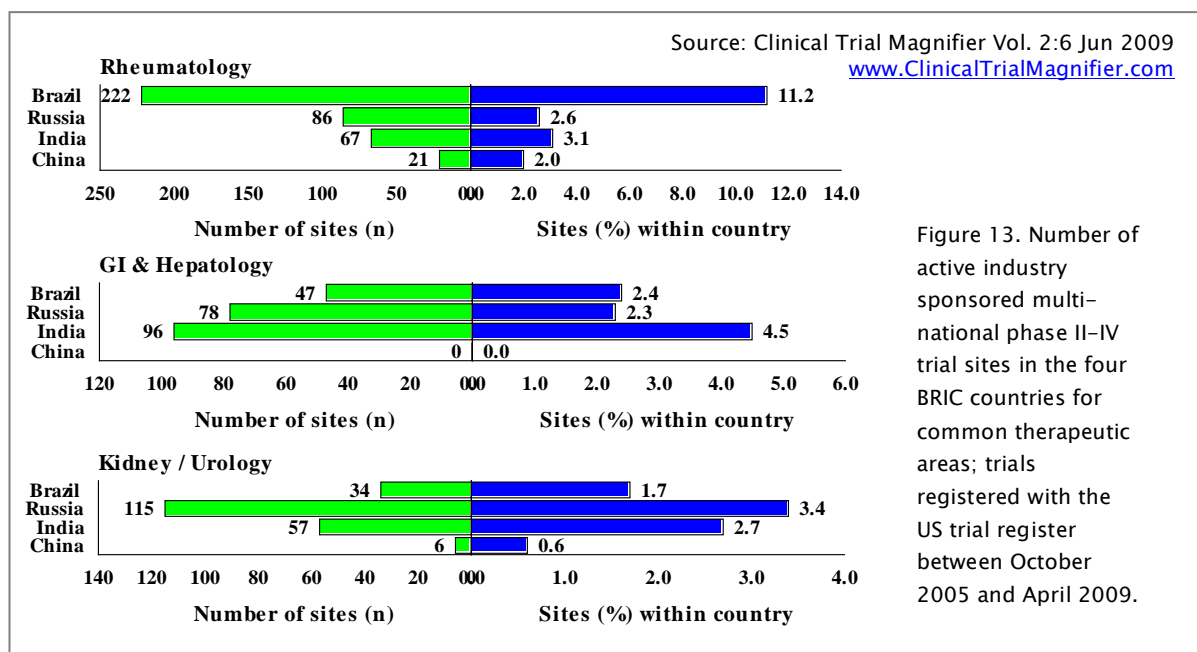


Figure 13. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for common therapeutic areas; trials registered with the US trial register between October 2005 and April 2009.

Table 4. Number of active - recruiting or ongoing - multi-national industry sponsored phase II-IV trial sites on drug and biologicals registered with the US trial register between October 2005 and April 2009 (43 months) for each of the four BRIC countries for the leading 20 diseases under trial.

Multi-national Recruiting/ongoing Disease	Brazil	Russia	India	China	Total	Brazil	Russia	India	China	Total
	Sites n	Sites n	Sites n	Sites n	n	Sites %	Sites %	Sites %	Sites %	%
Cardiovascular Heart	285	408	246	174	1,113	14.3	12.1	11.4	16.7	13.0
Endocrinology Diabetes/Glucose	146	318	319	62	845	7.3	9.5	14.8	5.9	9.9
Oncology Lung	121	257	121	69	568	6.1	7.6	5.6	6.6	6.6
Oncology Breast	147	190	109	62	508	7.4	5.6	5.1	5.9	5.9
Respiratory COPD	22	141	88	32	283	1.1	4.2	4.1	3.1	3.3
Cardiovascular Thrombosis	33	118	59	38	248	1.7	3.5	2.7	3.6	2.9
Rheumatology Arthritis	135	66	35	2	238	6.8	2.0	1.6	0.2	2.8
Cardiovascular Venous	66	44	56	62	228	3.3	1.3	2.6	5.9	2.7
Cardiovascular Stroke	43	69	27	84	223	2.2	2.1	1.3	8.0	2.6
Oncology Prostate	38	68	50	22	178	1.9	2.0	2.3	2.1	2.1
CNS Schizophrenia	30	88	51	0	169	1.5	2.6	2.4	0.0	2.0
Oncology Lymphoma	50	58	34	23	165	2.5	1.7	1.6	2.2	1.9
Cardiovascular Hypertension	48	69	32	14	163	2.4	2.1	1.5	1.3	1.9
Oncology Renal	15	99	17	21	152	0.8	2.9	0.8	2.0	1.8
Respiratory Embolism	33	27	35	29	124	1.7	0.8	1.6	2.8	1.5
CNS Depression	2	33	63	24	122	0.1	1.0	2.9	2.3	1.4
CNS MS	5	93	18	0	116	0.3	2.8	0.8	0.0	1.4
Oncology Leukemia	21	52	28	8	109	1.1	1.5	1.3	0.8	1.3
Rheumatology SLE	36	20	32	19	107	1.8	0.6	1.5	1.8	1.3
Kidney/Urology Kidney Chronic/Failure	6	71	29	0	106	0.3	2.1	1.3	0.0	1.2

to pass 50% of the total; and in Brazil, four leading cites.

Taipei, Taiwan (n=366) accounts for about the same number of active local and multi-national sites as Beijing (n=358). Hong Kong, with 276 sites, has a similar level of activity to Shanghai (n=234).

Two cities stand out for trial activity in the four BRIC countries. They are Moscow and St. Petersburg in Russia, with 1,049 and 839 sites, respectively. Sao Paulo (n=516) ranks third, ahead of Beijing (n=358).

Discussion

Growth

The four BRIC countries only contribute 5.9% of all industry sponsored phase II-III clinical trial sites globally, based on US trial register data over three years, i.e. 2006-2008. Russia's share is 2.3%, followed by India (1.5%), Brazil (1.3%) and China (0.8%).¹ Together, the four account for 22.2%, or one-in-five, sites in all emerging regions. Lately, however, a significant shift has been noted in the number of sites from North America and Europe to the emerging regions. This shift corresponding to 4.3% represents a total of 6,492 sites. About a third of these "new" sites

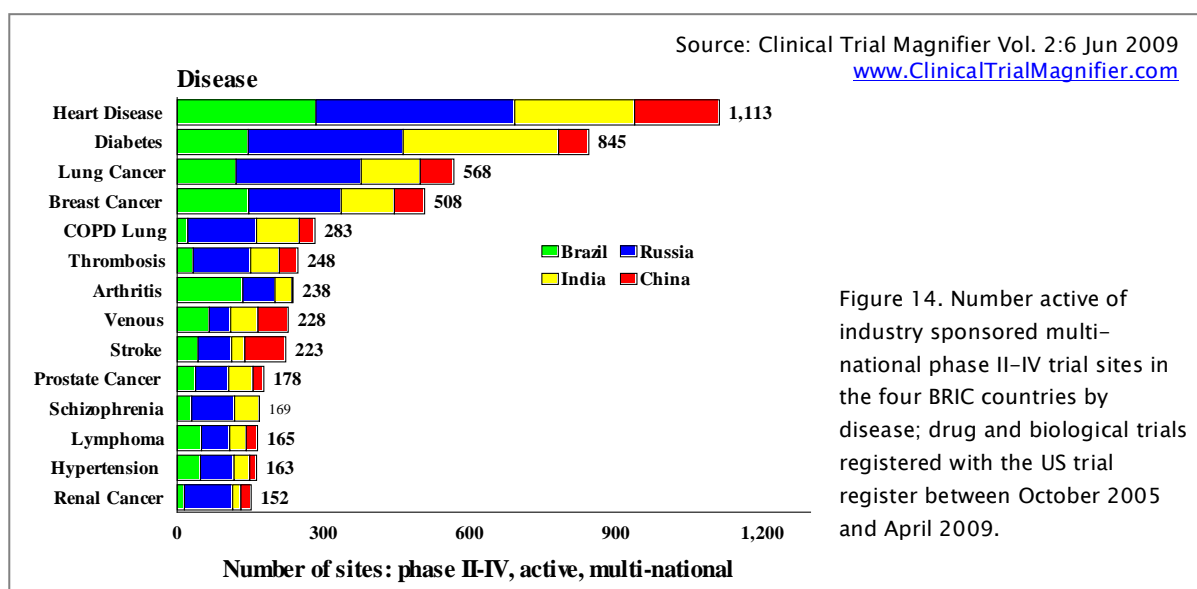


Figure 14. Number active of industry sponsored multi-national phase II-IV trial sites in the four BRIC countries by disease; drug and biological trials registered with the US trial register between October 2005 and April 2009.

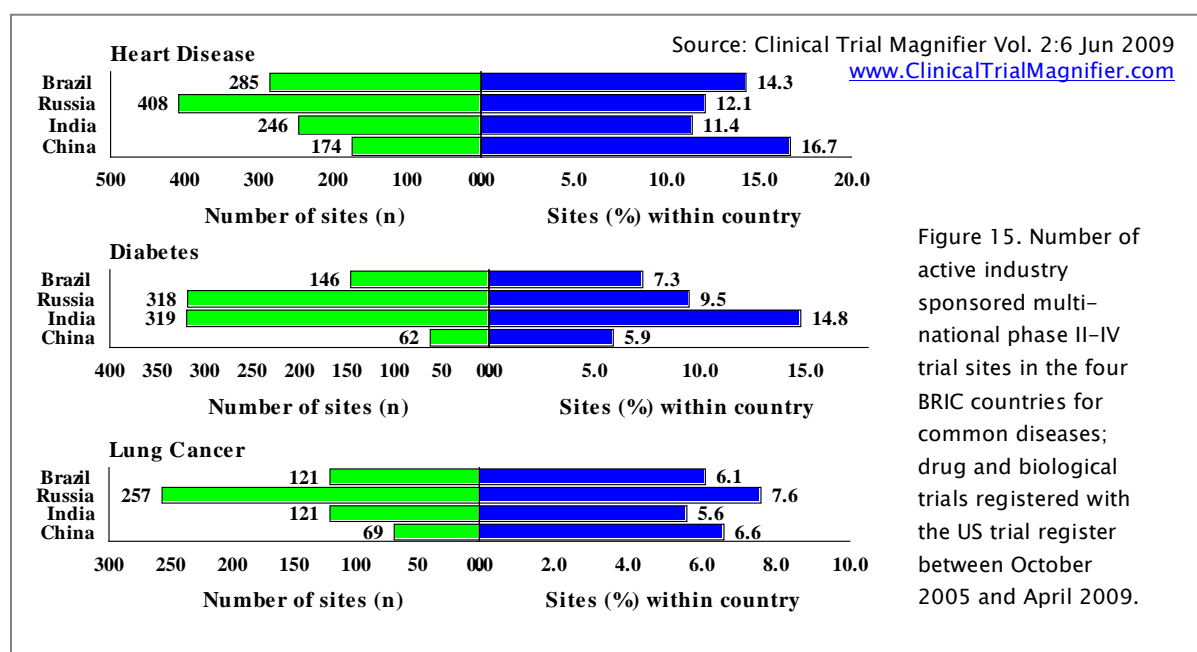


Figure 15. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for common diseases; drug and biological trials registered with the US trial register between October 2005 and April 2009.

– or 1.44% of them moving to – emerging countries – were located to the four BRIC countries. Russia captured an extra 0.5% of the global number of sites, India 0.5%, Brazil 0.26% and China 0.18%. It is therefore apparent that the industry is directing more and more trial sites to emerging countries – and especially to the four BRIC countries.

Over the past few years, all four BRIC countries have climbed in their global rankings for industry sponsored trial sites. Russia has risen from 10th to 9th, India from 18th to 12th, Brazil from 20th to 14th, and China from 27th to 23rd.¹ This trend is expected to continue, leading to Russia soon ranking above both UK and Italy, India above Australia, Brazil above

Belgium and China above Sweden.

Multi-national versus local trials and sites/protocol

Only about 6–7% of all sites in Russia, India and Brazil are local trials, conducted in one single country. On the other hand, close to half the trials and a quarter of sites in China are local in nature, reflecting insistence by the regulatory authority – the China State Food and Drug Administration (SFDA) – on conducting local registration trials.

The vast majority of the sites in all four BRIC countries are related to phase III multi-national trials, with the

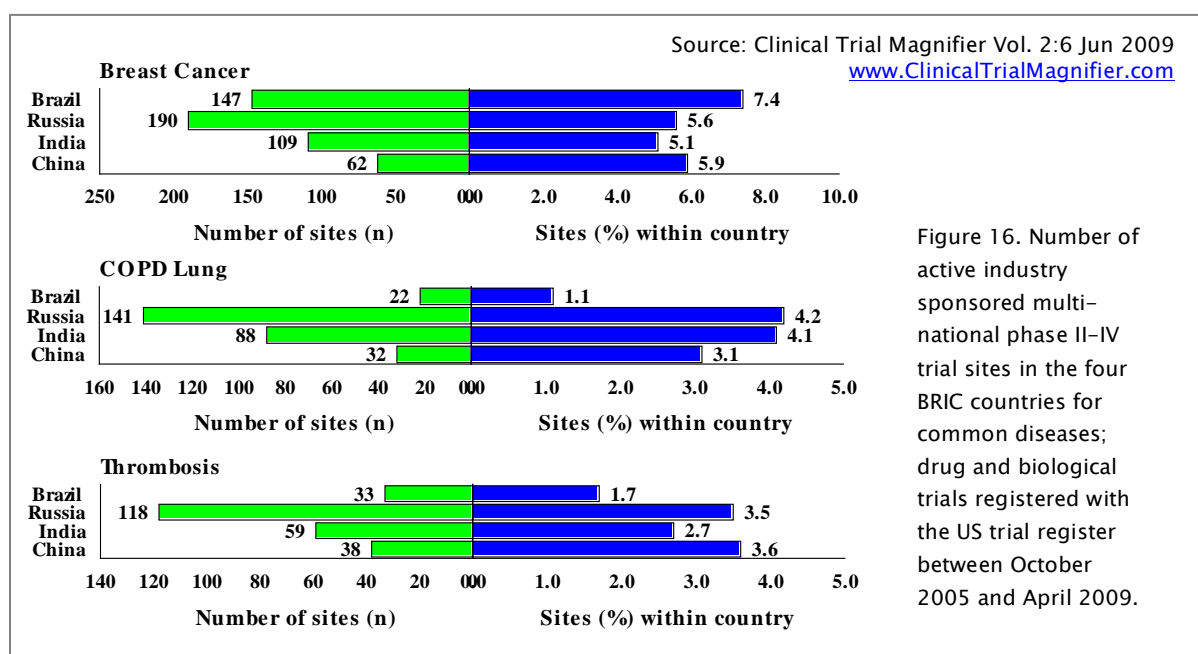


Figure 16. Number of active industry sponsored multi-national phase II–IV trial sites in the four BRIC countries for common diseases; drug and biological trials registered with the US trial register between October 2005 and April 2009.

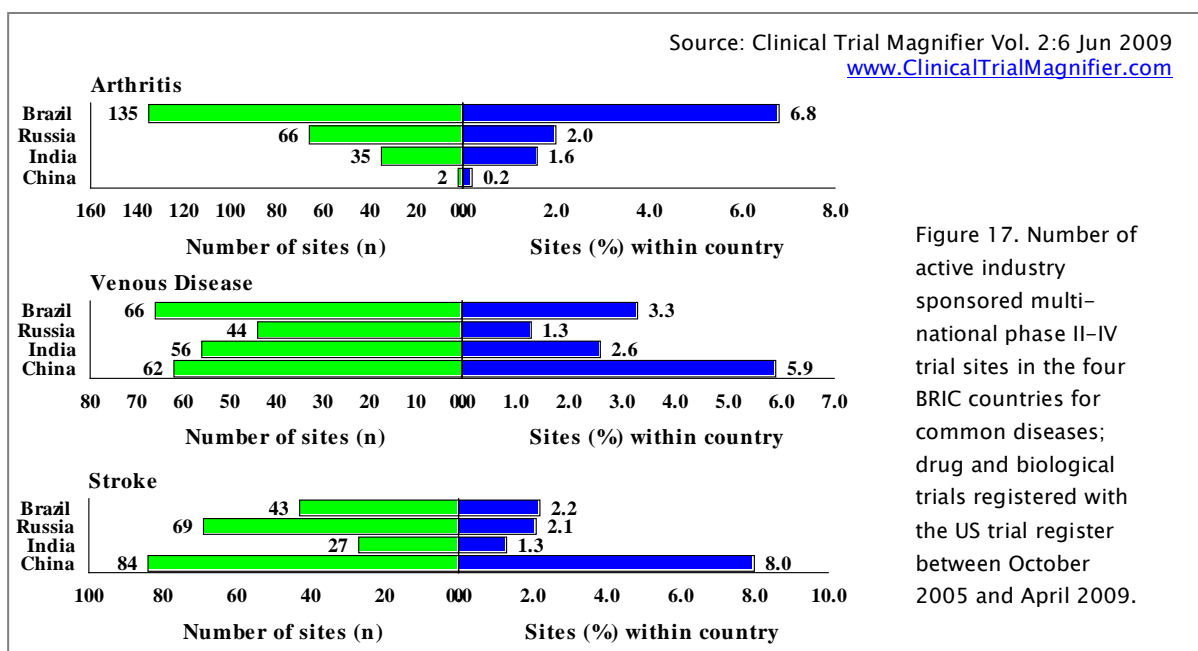


Figure 17. Number of active industry sponsored multi-national phase II–IV trial sites in the four BRIC countries for common diseases; drug and biological trials registered with the US trial register between October 2005 and April 2009.

number of sites per trial averaging between 6.9 in Brazil and 9.4 in China. The industry is clearly selecting emerging countries with large populations so many sites can be initiated for one and the same protocol. This is clearly an efficient use of resources, compared with smaller-populated countries, since the same project management and monitoring team can oversee all sites in an individual country. For instance, Singapore, with a population of 4.6 million, and Hong Kong with 7 million, average under two sites per trial.^{7,8} Notably, one US company, Eli Lilly and Company, recently withdrew a trial completely from Hong Kong because it could only contract one out of four potential sites.

Russia second to none

Russia is much more active in the industry sponsored trial arena than any of the three other BRIC countries. The only other emerging country close to Russia is Poland.¹ Moscow alone accounts for the same number of multi-national trials sites as all of China and St. Petersburg runs closely behind Moscow. It is not immediately apparent why Russia has developed so strongly. An explanation for this success is clearly of great interest. Generally, clinical trial approval time, patient population size, site performance and size of trial budgets are all important factors when selecting trial site locations. But in these, does Russia respond to the needs of the industry more than, for instance, India and Brazil?

China still in transition

With a population of over 1.3 billion representing more than a quarter of the world's population, China should have the potential to be a leading location for industry sponsored clinical trials. But China does not even outnumber Sweden, with a population of 9 million, or Israel with 7.1 million, in multi-national trial sites.¹ Two main reasons explain China's relatively poor performance – and neither are related to any bias on the part of the international pharmaceutical industry, which regards China as very important not only for clinical testing of medicinal products, but also as the largest emerging market for life science products. Many large international companies have also established pre-clinical development plants in China for drug discovery research. However, the infrastructure for industry sponsored clinical trials has as yet not been fully addressed in China.

The most important reason for the remarkably low trial activity in China is the time it takes to receive approval for conducting trials. Approval is granted by the SFDA and according to many industry representatives takes on average 9–12 months, compared with 2–4 months in most other countries. This exceptionally long approval time is reflected by the low proportion of phase II trials in China. Only 9.2% of multi-national phase II and III trials in China are phase II, compared with 24.2–34.2% in the other three BRIC countries. Since many phase II trials are

Table 5. Number of active – recruiting or ongoing – multi-national industry sponsored phase II–IV trial sites on drug and biologicals registered with the US trial register between October 2005 and end of April 2009 (43 months) for each of the four BRIC countries for the 20 most active industry sponsors.

Multi-national Recruiting /ongoing Company	Brazil Sites n	Russia Sites n	India Sites n	China Sites n	Total n
Bristol-Myers Squibb	312	413	282	90	1,097
Hoffmann-La Roche	398	299	10	120	827
Boehringer Ingelheim	64	332	239	104	739
GlaxoSmithKline	137	288	164	125	714
Bayer	140	119	89	236	584
AstraZeneca	117	72	89	88	366
Pfizer	119	109	80	44	352
Johnson & Johnson	20	207	96	24	347
Eli Lilly	101	46	123	43	313
Novartis	52	95	84	17	248
Eisai	24	77	45	0	146
Wyeth	25	42	46	28	141
Schering-Plough	73	9	25	21	128
Sanofi-Aventis	25	32	28	10	95
Takeda	15	47	26	0	88
KV	0	49	32	0	81
Biogen	0	33	42	0	75
Poniard	0	51	24	0	75
Amgen	20	18	33	0	71
EMD Serono	13	45	7	3	68

short in duration, they can in most cases be completed in other countries before applications are even approved by China's SFDA.

The second reason China has not yet made a significant impact internationally is a shortage of acceptable and experienced investigators. China has about two million physicians, but only some 2,000 study sites are accredited by the SFDA to conduct clinical trials on new medicinal products aiming to be registered in China.⁹ According to a discussion at a recent conference only about 40% of sites accredited by the SFDA are in fact up to acceptable standard. It was also suggested there are many high performing sites in China that for one reason or another have not

obtained accreditation, and can thus not be selected for trial participation.

Many actively promote China as a leading and even established location for clinical interventional trials. But the facts simply do not support such conclusions. It is also difficult to identify any apparent movement towards bureaucratic change in China, enabling the most populated country on earth to play its deserving role in clinical testing, and advance up the rankings of the most active emerging countries – from its currently position behind Russia, Poland, Australia, India, Brazil, Argentina, Czech Republic, Hungary, Mexico, Ukraine and South Africa.¹

While representing predominantly Chinese

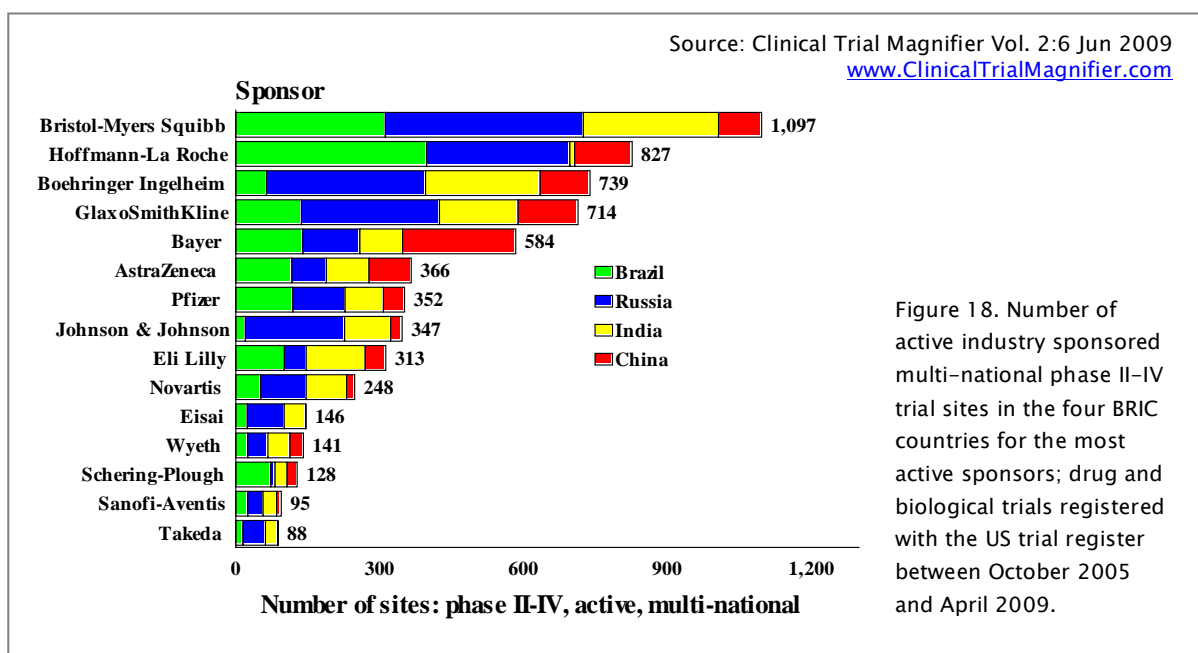


Figure 18. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for the most active sponsors; drug and biological trials registered with the US trial register between October 2005 and April 2009.

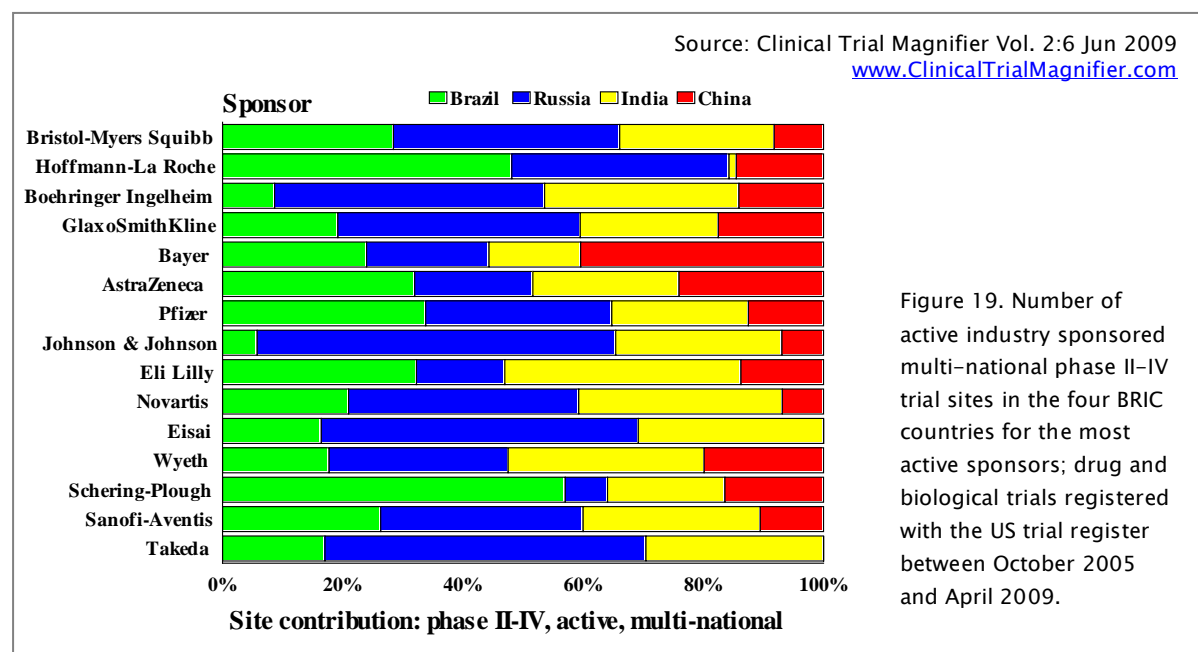


Figure 19. Number of active industry sponsored multi-national phase II-IV trial sites in the four BRIC countries for the most active sponsors; drug and biological trials registered with the US trial register between October 2005 and April 2009.

populations, China, Taiwan and Hong Kong each have their own drug regulatory authority and regulations. Taiwan and Hong Kong – with a combined population of about 30 million – have about the same number of multi-national trial sites as the whole of China. Regulatory frameworks and investigator availability are seemingly at present more acceptable in Taiwan and Hong Kong than in mainland China.

Active trials

This study defined the number of trials and related sites based on active phase II–IV trials – with ‘active’

here defined as trials under recruitment of subjects or ongoing trials with follow up of subjects. Those represent 68.8% of all phase II–IV trials. Most of the remaining trials (28.1%) had been completed. The ‘active trial’ definition was adopted because it more realistically illustrates ongoing activities, rather than past activity. This means that numbers here do not precisely match those provided in other studies based on the US trial register data. Data here also differ from other studies by including trials registered over a longer period of time (43 months).

Table 6. Number of active – recruiting or ongoing – industry sponsored phase II–IV trial sites on drug and biologicals registered with the US trial register between October 2005 and April 2009 (43 months) for the most active cities within the four BRIC countries; all cities with 50 or more active sites are included.

Country	City	Sites	Sites	Total n	Sites within
		Local n	Multi-national n		Country %
Brazil	Sao Paulo	37	479	516	26.0
Brazil	Porto Alegre	13	288	301	15.1
Brazil	Rio De Janeiro	10	171	181	9.1
Brazil	Curitiba	7	138	145	7.3
Brazil	Belo Horizonte	10	97	107	5.4
Brazil	Campinas	9	96	105	5.3
Brazil	Goiania	2	80	82	4.1
Brazil	Salvador	6	65	71	3.6
Brazil	Santo Andre	3	60	63	3.2
Brazil	Fortaleza	2	50	52	2.6
China	Beijing	93	265	358	34.3
China	Shanghai	60	174	234	22.4
China	Guangzhou	30	94	124	11.9
China	Nanjing	26	51	77	7.4
China	Hangzhou	15	52	67	6.4
China	Wuhan	14	44	58	5.6
China	Xian	20	33	53	5.1
India	Bangalore	14	212	226	10.5
India	Mumbai	12	203	215	10.0
India	New Delhi	13	171	184	8.6
India	Pune	9	166	175	8.1
India	Hyderabad	7	113	120	5.6
India	Chennai	7	101	108	5.0
India	Jaipur	5	82	87	4.0
India	Ahmedabad	5	77	82	3.8
India	Calcutta	12	55	67	3.1
India	Mangalore	0	58	58	2.7
India	Lucknow	3	50	53	2.5
Russia	Moscow	49	1,000	1,049	31.2
Russia	St. Petersburg	37	802	839	24.9
Russia	Yaroslavl	5	120	125	3.7
Russia	Novosibirsk	5	100	105	3.1
Russia	Kazan	6	88	94	2.8
Russia	Ekaterinburg	11	75	86	2.6
Russia	Nizhniy Novgorod	7	75	82	2.4
Russia	Saratov	5	66	71	2.1
Russia	Samara	3	62	65	1.9
Russia	Tomsk	4	60	64	1.9
Russia	Chelyabinsk	5	53	58	1.7
Russia	Smolensk	2	51	53	1.6
Russia	Krasnodar	6	44	50	1.5

Therapeutic area and diseases

In a previous study exploring trends in therapeutic area and disease focus in drug development, we found that oncology, CNS, cardiology, infectious, endocrinology and respiratory were the most active therapeutic areas under trial by the pharmaceutical industry.¹⁰ Those therapeutic areas are also the top six under trial in the four BRIC countries, with oncology and cardiology accounting for over 50% of sites. The disease pattern is also very similar for the four BRIC countries with diabetes, hypertension, asthma, hepatitis, breast cancer, asthma and lung cancer being the most active.

It can therefore be concluded there is no major difference between type of trials conducted in the four BRIC countries and elsewhere. However, some differences are noteworthy *among* the four countries. For instance, relatively more cardiovascular, hepatitis and liver cancer trials are conducted in China, more diabetes trials in India, and more arthritics trials in Brazil. Such differences certainly reflect geographic differences in disease prevalence, but probably also drug development portfolio variations among companies, along with their different country preferences.

Sponsors

Major pharmaceutical companies demonstrate large differences between their levels of trial activities in the BRIC regions. AstraZeneca, Pfizer, Johnson & Johnson, Eli Lilly, Novartis and Wyeth all have fewer than half

the sites of Bristol-Myers Squibb, Hoffmann-La Roche, Boehringer Ingelheim and GlaxoSmithKline. Some are highly active in Russia, while others – namely Hoffmann-La Roche, AstraZeneca and Pfizer – are more active in Brazil. Bayer stands out with the most BRIC region sites in China. Takeda and Amgen have no activity in China at all. Clearly, geographic diversity exists in level of activity among major sponsors in the four BRIC countries. It would be of great interest to find out the main reasons for this diversity or internal policy.

Cities and patterns

Moscow and St. Petersburg in Russia stand out as the leading BRIC region cities. In a previous study, we reported that Moscow ranked 11th among all cities worldwide and St. Petersburg 24th.¹¹ Since then, it is likely those rankings have improved for both cities. Only 18 months ago, Moscow accounted for more industry sponsored trial sites than every capital in Europe except Paris, surpassing the likes of Berlin, Madrid, London and Rome.

Another point of interest is that in both China and Russia, two cities dominate (together accounting for >50% of sites in their respective countries). This dominance is only achieved by combining the top seven cities in India, and four most active in Brazil. Based on this, India has an apparent advantage over the other three BRIC countries, since the infrastructure to handle industry sponsored trials is clearly in place in a larger number of locations/cities. Since it can be assumed the industry will strive to involve sites

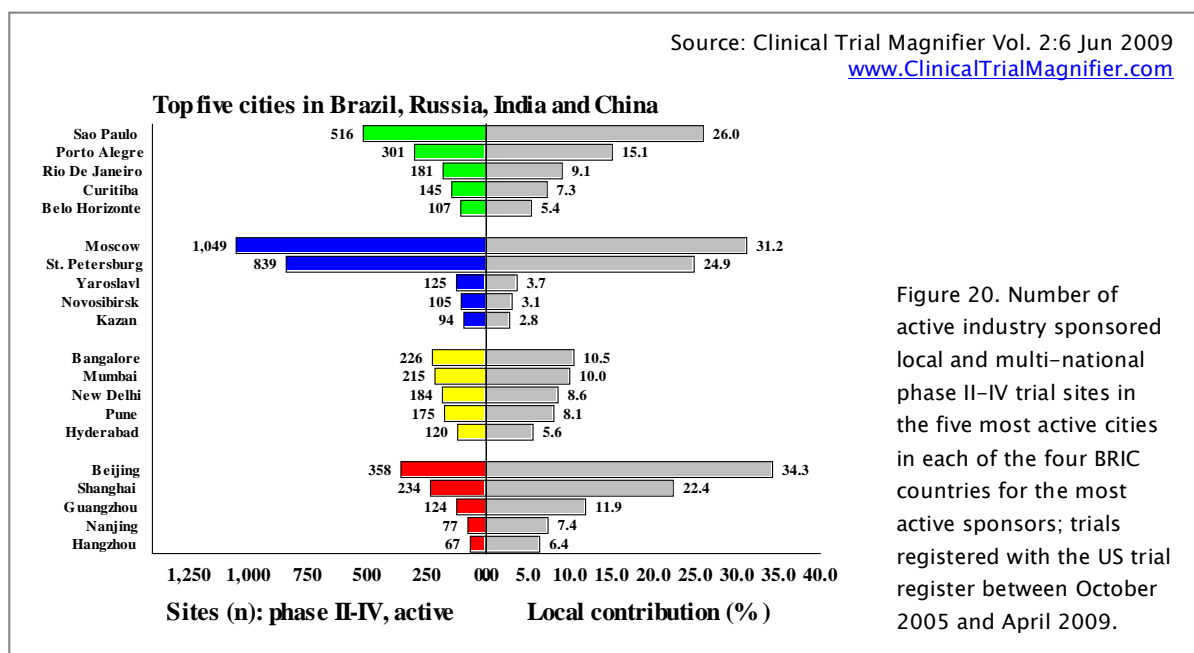


Figure 20. Number of active industry sponsored local and multi-national phase II-IV trial sites in the five most active cities in each of the four BRIC countries for the most active sponsors; trials registered with the US trial register between October 2005 and April 2009.

outside the main institutions/cities in emerging regions, demand seems likely to increase for infrastructure development, by training investigators and assisting to develop efficient and high standard ethics committees.

Conclusions

The four BRIC countries represent 60% of the world population but contribute as little as 5.9% of all active industry sponsored sites globally. The four hold enormous potential to become major players in international clinical research. The industry prefers to locate large phase III trials to the four BRIC countries for the most popular diseases under clinical testing. A continuing drift of study sites can be expected from North America and Europe to emerging countries and especially the BRIC regions. A clear exception is China. A strict and conservative regulatory framework plus shortage of experienced, accredited investigators/sites undermine China's potential to significantly advance in the international clinical research playing field, and to challenge the other three BRIC countries.

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WHY IS RUSSIA STANDING OUT? THE MAGNIFIER ASKS THE EXPERTS..

Interview with Dr. Maxim Belotserkovsky – Senior Director Medical Affairs and Head Medical Affairs of PSI CRO AG

Magnifier: Can you please outline key information about PSI?

“PSI is a full-service CRO with offices across Europe and the Americas, specializing in clinical drug development in all major therapeutic areas.

The company has been around since 1994 and is headquartered in Zug, Switzerland. The number of staff is at present 850, with offices located in Switzerland, USA, Russia, Ukraine, Poland, Romania, Bulgaria, Serbia, Hungary, Austria, Argentina and Estonia.

The company opened its first Russian office in 1994 and has at present approximately 400 employees in Russia. PSI has completed about 250 protocols in Russia with about 60 ongoing protocols.”

Magnifier: What type of clients are your company collaborating with in Russia?

“We have never collaborated with a Russian client. We have been involved in clinical studies for the US, EU, and Japanese pharmaceutical and biotech companies.”

Magnifier: In your view, what are the reasons that Russia is much more active in industry sponsored clinical trials than the other three BRIC countries?

“I think that there are three main reasons for that:

- *The main one is that international industry-sponsored clinical trials came to Russia probably earlier than to most of the other BRIC countries, except perhaps Brazil. Global pharmaceutical companies started involving Russian investigators in clinical projects in the early 1990s. So our investigators have extended exposure to clinical trials. They*

developed adequate skills and knowledge as well as a good reputation among sponsors.

- *The second reason is creativity and eagerness to investigate new products, which is a typical trait of the national character (I think). That’s why we have really strong scientific schools, and scientists and investigators are publicly appreciated.*
- *Last but not least is a public healthcare system inherited from the Soviet era. Our healthcare system is centralized and patients naturally gravitate to a limited number of specialized clinics/centers. Patients are data based in these centers and it’s easier to enroll them into studies.”*

Magnifier: Will Russia continue to be the leading BRIC country, or will any of the other three BRIC countries catch up?

“I think Russia will remain one of top ten countries involved in clinical research for the next five years, or even a decade. But at the same time I believe that China, by implementing a systematic approach with governmental support to clinical research, has very good chances to catch up and even outrun us. In the long term, India also has good chances to catch up with Russia, providing it sustains stable economic growth.”

Magnifier: Why are the majority of Russian sites centred in Moscow and St. Petersburg, not other cities?

“There are two main reasons:

- *The first is that most Russian clinics are concentrated in Moscow and Saint Pete, and their suburbs, which together have a population of around 21 million, a seventh of all Russia’s population.*
- *The second point is logistics. Conduct of clinical trials implies inbound and outbound shipments of fragile clinical trial materials and bio-samples. In Russia, such shipments can be practically cleared in Moscow and Saint Pete. For most trials, the time of transportation is critical, that’s why we have to use sites in Moscow and St. Petersburg in many studies. One more reason is that now in Russia, almost all global CROs and big pharmaceutical companies are in Moscow and St. Petersburg, and few go elsewhere.”*

Magnifier: re there any specific incentives in Russia for physicians and trial subjects to participate in industry sponsored trials?

“Undoubtedly, industry-sponsored clinical research is about money. But on top of that, Russian investigators are extremely sensitive about being engaged in scientific work, they are proud of being listed in publications and participating in international professional meetings/conferences/congresses.

Our patients in most cases are also motivated by the possibility of receiving state-of-the-art treatment and the chance to be treated by the most professional physicians.”

Magnifier: Are there any aspects of clinical research that can be improved in Russia?

“I think any aspect of clinical trials can be improved and needs some improvement. You may name any aspect and I will suggest my ways of improvement, but this can be discussed endlessly.

There is the only aspect I would like to have as it is, and not change. This is our investigators' motivation to participate in trials and their dedication and dependability.”

Interview with Dr. Sumit Seth – Managing Director in Russia for TFS Trial Form Support

Magnifier: Can you please provide some key information about TFS?

“Dr. Daniel Spasic instituted TFS in 1997 in Lund, Sweden and it is still headquartered in Lund. The company has approximately 500 staff and offers all the services needed for drug development projects. TFS has offices in Russia, Sweden, Finland, Norway, Denmark, The Netherlands, UK, Spain, Portugal, Hungary, Poland, Estonia, USA, India and Japan.

The first Russian office opened in 2006 and we have at present 12 staff in Russia. The company has completed 11 trials in Russia with three ongoing.”

Magnifier: Why do you think Russia is much more active in industry sponsored clinical trials than the other three BRIC countries?

- *“Leadership,*
- *Very well developed and centralized health care system,*
- *Well defined regulatory procedures,*

- *Availability of experienced investigators,*
- *Closeness to clients, and*
- *Access to Caucasian patients.”*

Magnifier: Will Russia continue to be the leading BRIC country or will any of the other three BRIC countries catch up?

“I believe that Russia will continue to be a leader due to the above-mentioned reasons and will not lose its values in the near future.”

Magnifier: Why are the majority of the sites located to Moscow and St. Petersburg and not other Russian cities?

- *“Leadership,*
- *These two cities alone are home to around 15 million people and together with their suburbs around 21 million. Hence the recruitment potential is huge, or at least enough for a typical Phase II or III trial,*
- *Connectivity to major cities around the world and hence all logistical issues are easier to manage, namely the import and sample export to central clinical laboratories,*
- *By confining to these cities, the travel costs are minimized without compromising the recruitment rate, and*
- *Most of the key opinion leaders are located in these cities.”*

Magnifier: Are there any specific incentives in Russia for physicians and trial subjects to participate in industry sponsored trials?

“No more incentives specific to Russia than anywhere else in the world.”

Magnifier: Are there any aspects of clinical research that can be improved in Russia?

“Shortening of regulatory approvals and removal of logistical hurdles.”