



REUTERS/Dylan Martinez

OVERCOMING CLINICAL CHALLENGES IN BRIC MARKETS

A WHITE PAPER



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INTRODUCTION

By 2017, China is expected to become the second largest pharmaceutical market in the world next to the United States⁽¹⁵⁾. Brazil, Russia, and India are not far behind. The Global Use of Medicines: Outlook through 2017 report from IMS Institute for Healthcare Informatics predicts a rise in ranks for each of the BRIC countries over the next four years, indicating blossoming healthcare budgets and markets ripe for drug development. The benefits to performing clinical trials in BRIC countries are numerous. A pool of almost 3 billion patients in concentrated research centers across major cities leads to fast recruitment and cost-effective trials. Increased spending on healthcare and R&D has fostered a growing number of educated and trained health professionals as well as investigational medicinal product manufacturers and central laboratories. Strengthening regulations means more governmental resources and defined pathways for approval. Despite the obvious benefits of performing trials in these

regions, however, drug development in most of the countries is on the decline (Fig 1A). The low-cost, high-demand climate should have global sponsors lining up to gain a foothold in the BRIC markets, but they are largely pulling back or out completely. Increasingly complex regulatory guidelines, corruption, patent challenge losses to generics, and import/export delays are clearing out foreign sponsors looking for viable sites. In their wake, untapped clinical sites abound, showcasing experienced investigators, top-of-the line diagnostic equipment, and good clinical practice (GCP) compliance. Although the regulatory red tape is becoming more complex as BRIC governments rise to meet Western standards, there are some companies who have managed to navigate it. The question is, how? How are they staying ahead of the ever-changing clinical regulatory landscape and running swift, cost-effective trials in BRIC countries?

5 YEAR LOOK AT NUMBER OF CLINICAL TRIALS STARTED IN BRIC COUNTRIES

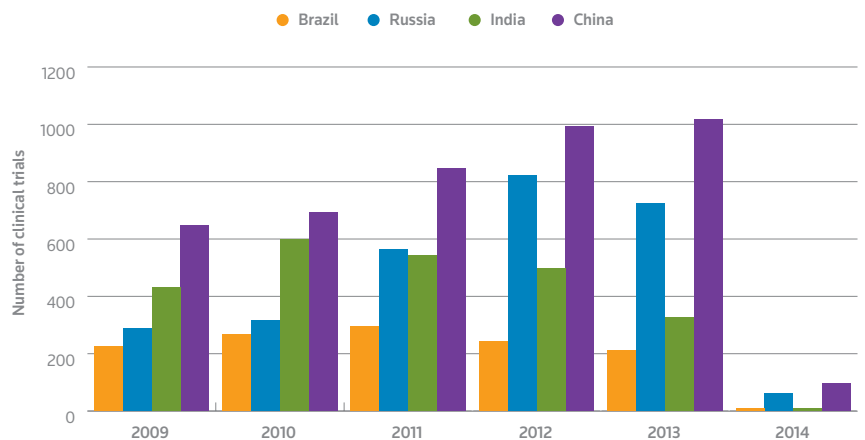


FIG 1A. NUMBER OF CLINICAL TRIALS STARTED PER YEAR IN BRIC COUNTRIES (CORTELLISTM CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

TOP 5 THERAPEUTIC AREAS FOR CLINICAL TRIALS IN BRIC COUNTRIES

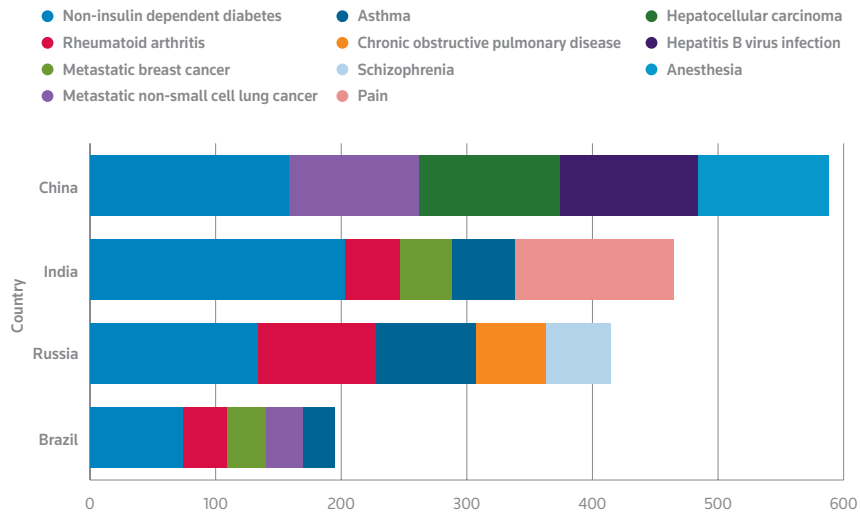


FIG 1B. NUMBER OF CLINICAL TRIALS STARTED PER YEAR IN BRIC COUNTRIES BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

CLINICAL TRIALS BY PHASE IN BRIC COUNTRIES

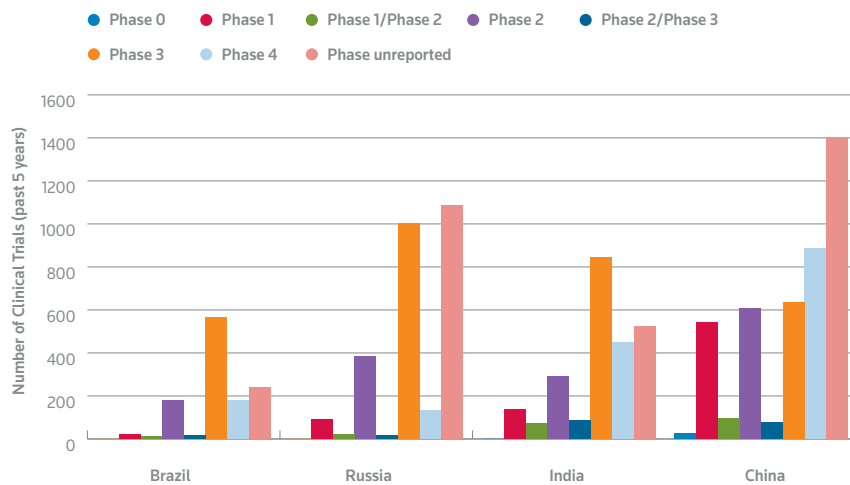


FIG 1C. NUMBER OF CLINICAL TRIALS STARTED PER YEAR IN BRIC COUNTRIES BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

BRAZIL

In 2012, Brazil ranked sixth in pharmaceutical spending. By 2017, IMS predicts that the country will rise to fourth, just behind Japan⁽¹⁵⁾. Ideally, performing clinical trials in Brazil averages a cost savings of 20 to 30 percent as compared to Western markets⁽¹¹⁾. Though Brazil boasts a national healthcare program, the Unified Health System (SUS), it is part of a tertiary-tier system with upwards of 25 percent of the population opting to purchase private insurance for access to second and third-tier care⁽³⁾. This has resulted in a large patient population with reduced access to beyond-basic level care, leaving potential subjects largely treatment-naïve. Urban areas such as Sao Paulo and Rio de Janeiro provide concentrated areas (over 87 percent of the population) of clinical opportunities and expertise. In fact, the growth rate of U.S. Food and Drug Administration (FDA)-regulated investigators from 2001 to 2010 is higher than that of the U.S. and the UK, as well as the rest of Latin America⁽¹¹⁾. The doctor-patient relationship is strong in the country and promotes not only participation in clinical trials, but retention as well.

Although improving, Brazil's regulatory approval process for clinical trials still remains the lengthiest in Latin America and can take anywhere from five to 12 months⁽²²⁾. ANVISA, the National Health Surveillance Agency for Brazil, operates much like the FDA in the U.S. and issues the Special Communicate, Brazil's official clinical approval document, as well as the import license for investigational drugs. In a complex and systematic approval process, the protocol is sent for approval to each planned site's ethics committee (CEP) as well as the coordinating site. Once approved by the coordinating site, it is sent to the National Commission for Ethics in Research (CONEP) for final ethics approval. As an improvement to this redundant system, ANVISA has recently implemented a simplified process - the sponsor need only to submit the protocol to the coordinating site's CEP for ethics approval. Once approved by the coordinating site, the protocol is simply agreed to be implemented at the other sites and is sent to CONEP for national approval. In further effort to decrease approval timelines, ANVISA will issue the Special Communicate and import license to the coordinating site which can then be implemented by each site upon approval by their ethics committee. In June 2012, a new measure was sought to reduce timelines even

more, particularly for foreign-run trials. If the clinical research has been approved by the FDA, the European Medicines Agency (EMA), Japan's Pharmaceutical and Medical Devices Agency, Australia's Therapeutic Goods Administration, Health Canada, or the study has recruited patients in other countries, the simplified procedure can be used. This route involves a single step where the clinical research application is sent directly to ANVISA and evaluated within three to four months on average (8). This new measure does not apply to vaccines and/or anti-retroviral drugs.

The rapidly changing clinical landscape, along with the current complexity and lengthiness of approval and import processes, have been cited as the biggest drawbacks in initiating clinical trials in Brazil. However, there are other reasons global sponsors have been pulling out of the country. Placebo trials require additional rationale and multiple reviews, increasing timelines and decreasing cost effectiveness. The compassionate use program, approved by ANVISA in August of 2013, guarantees free orphan drug supply to those who have participated in a phase III trial and benefitted from the drug. Because the patient population for a rare disease is limited by nature, the sponsor's Brazilian market for the respective orphan drug may be entirely comprised of its successful phase III trial patients, negating any profit they may make in the country.

Overall, trials have declined in Brazil since 2011 (Fig 1A). As big pharma threatens to recede from the country, local companies are filling the gaps; university and government trials have been increasingly dotting the clinical landscape. BRIC powerhouse Novartis remains a key player in the country, along with Roche and AstraZeneca. Pfizer, Sanofi, and GlaxoSmithKline (GSK) have exhibited a decreasing presence in the top 10 sponsors performing clinical trials since Brazil's peak in 2011. In evaluating pioneer conditions, those conditions in which therapeutics are being evaluated for the first time, it can be seen that they are mostly being initiated by big pharma with a couple local sponsors in the mix (Fig 2B). The pioneer conditions are diverse with a small concentration in cardiovascular disease (Fig 2C).

Top therapeutic areas of trials started in Brazil in the past five years include non-insulin dependent diabetes and rheumatoid arthritis, leaving opportunities in oncology and cardiology (Fig 2D). Early phase trial patient pools and sites remain relatively open as phase III trials make up most of those being initiated (Fig 2E).

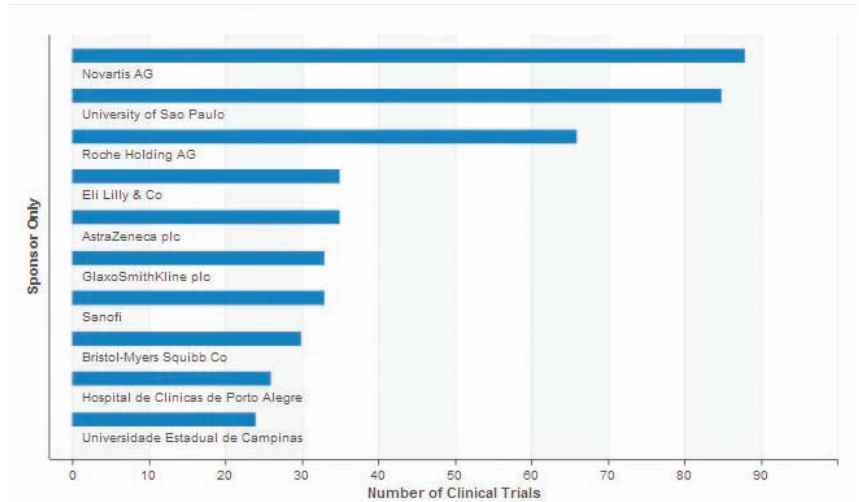


FIG 2A. NUMBER OF CLINICAL TRIALS INITIATED IN BRAZIL FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

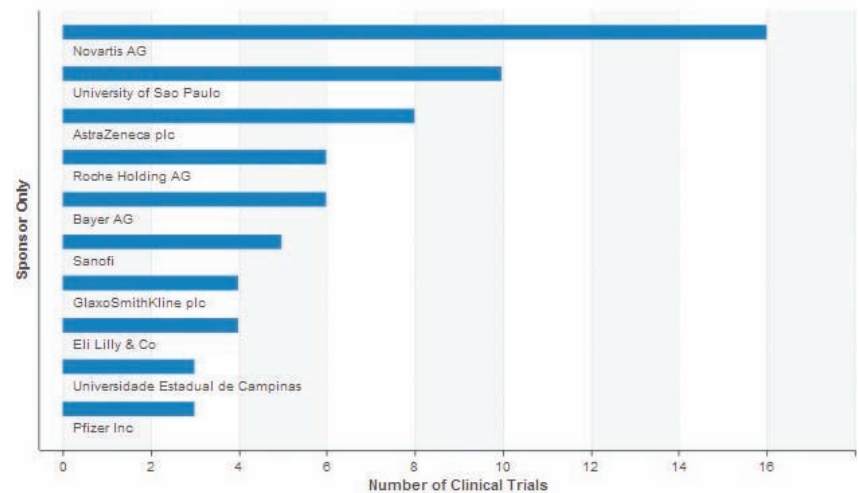


FIG 2B. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN BRAZIL FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

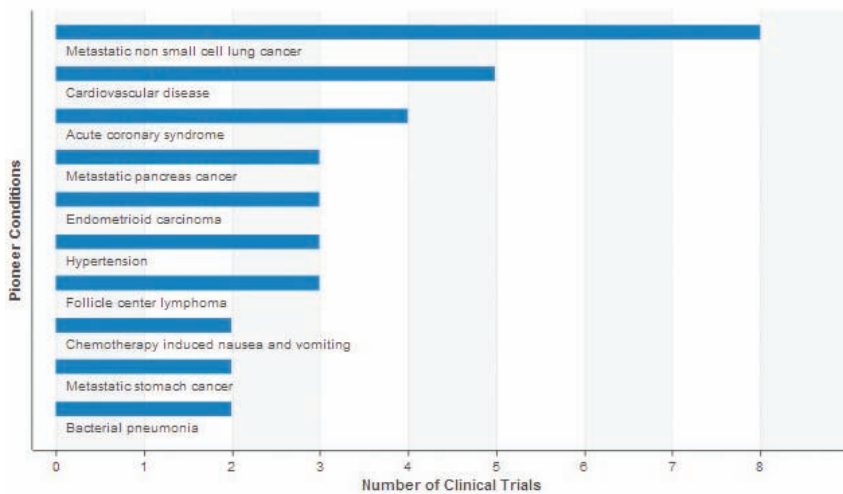


FIG 2C. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN BRAZIL FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

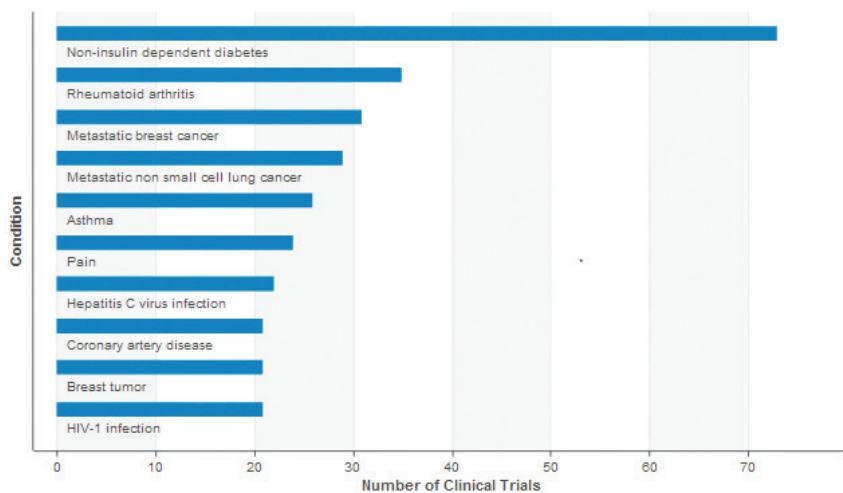


FIG 2D. NUMBER OF CLINICAL TRIALS INITIATED IN BRAZIL FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

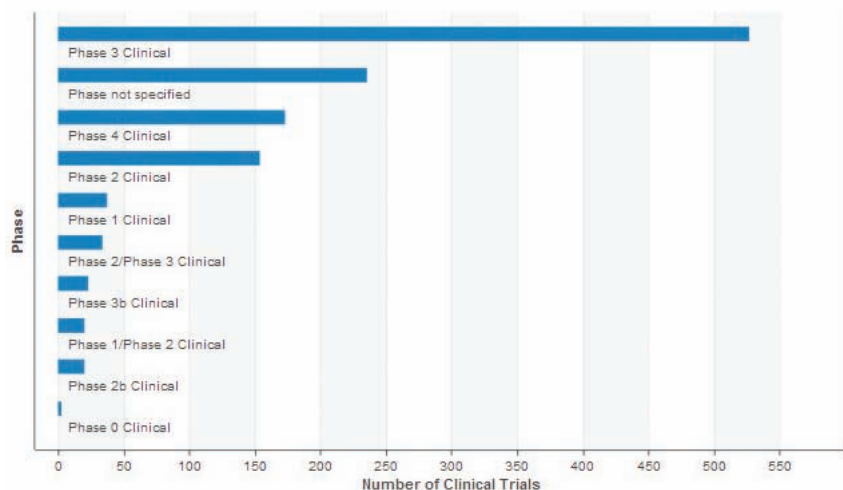


FIG 2E. NUMBER OF CLINICAL TRIALS INITIATED IN BRAZIL FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

RUSSIA

Slated to rise from 11th to eighth place in the global pharmaceutical rankings⁽¹⁵⁾, Russia is steadily proving to be a lucrative market for investors. With increased healthcare expenditure and governmental support of innovation through the implementation of Strategy 2020, policy-making and industry reform are shaping Russia's drug development landscape. Efforts to localize pharmaceutical manufacturing and increase domestic R&D standing have been successful. Most of large pharma has set up camp in the country and remains present despite a drop in clinical trials in 2013. With an "on-the-ground" presence, sponsors are able to take advantage of the benefits to running clinical trials in Russia. Although modernizing, with plans for a large-scale reform being implemented, the national healthcare system of Russia remains inadequate. Compulsory Health Insurance is intermixed with private insurance and most feel the system is complex and inefficient. Citizens complain of a lack of trust and funding, leaving them with high out-of-pocket expenses. This disengagement from the healthcare system results in a large, mostly treatment-naïve patient pool concentrated in major cities, namely Moscow and St. Petersburg, and other benefits such as fast enrollment and patient retention. As Putin's healthcare reform takes shape, however, the quality of medical institutions and clinical laboratories is increasing. In 2013, the FDA conducted two clinical trial inspections in Russia; both passed with only voluntary actions suggested. This speaks to the high quality of clinical data produced in the country as well as the training and performance of its investigators. Despite their expertise, Russian investigators experience lower grant funding and require lower fees than their Western counterparts. With an average cost-savings of 60 to 70 percent per clinical trial patent (24), it is easy to see why big pharma is growing roots in Russia.

The Ministry of Health of the Russian Federation (MoH) accredits medical institutions in the country (ensuring ICH-GCP compliance), approves preclinical and clinical trials, and grants import/export licenses for investigational drugs and biological samples. A clinical trial application must go through the MoH where it is then submitted

to the Ethics Board and to the Federal State Institution “Scientific Center of Medicines Expertise of RZN” (FSI SCMER) for scientific review. Once approved, the application receives the go-ahead from the local ethics committee of each participating medical institution. As the trial is underway, the Federal Surveillance in Healthcare (Roszdravnadzor – RZN) performs assessments, as well as maintains the clinical trials database and ensures pharmacovigilance and risk management.

While change, especially in emergent countries like Russia and India, is both coveted and necessary, the upheaval of the healthcare system and the tumultuous regulatory landscape are seen as primary barriers to clinical development in Russia. Sponsors and contract research organizations (CROs) argue that it is difficult to keep up with consistently changing regulations, causing delays in trial timelines and decreasing the expected cost-effectiveness. Current timelines in Russia average three to four months. Unethical conduct is another caveat in the country as revealed in several surveys and remarks by pharma. Biogen Idec provided an example at the Global Clinical Trials Conference: in 2013, the company shut down all sites for a phase II trial (one quarter of the study’s patients) in Russia, because investigators did not want their trial income reported to the state employers.

Although it does not appear that global sponsors are largely pulling out of Russia, clinical trial initiation has declined in number since its peak in 2012 (Fig 1A). Novartis and GSK maintain a strong presence, while Eli Lilly, Pfizer, Sanofi, and Bristol-Myers Squibb have been edged out of the top 10 by Teva and domestic Russian pharmaceutical companies Atoll, Vertex, and Biocad (Fig 3A). Russia’s pioneer condition trials continue to be dominated by big pharma with Biocad making an appearance (Fig 3B). Conditions are diverse, with a small concentration in oncology (Fig 3C).

Top conditions studied in new trials over the past five years in Russia include non-insulin dependent diabetes, rheumatoid arthritis, and pulmonology (Fig 3D). As phase I trials must be run in Russia, the majority of foreign trials being started in the country are phase II and III (Fig 3E). Most phase I trials are being initiated by domestic Russian companies or foreign sponsors with a local presence, such as Novartis, Teva, Roche, and Boehringer Ingelheim.

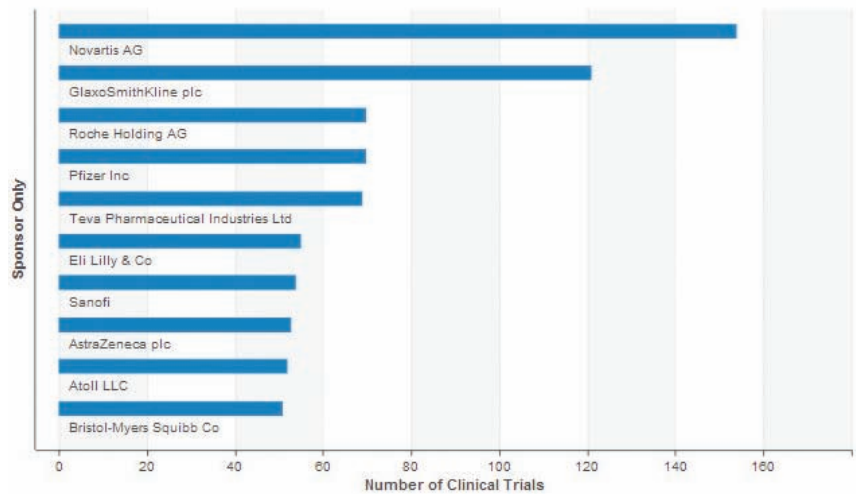


FIG 3A. NUMBER OF CLINICAL TRIALS INITIATED IN RUSSIA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

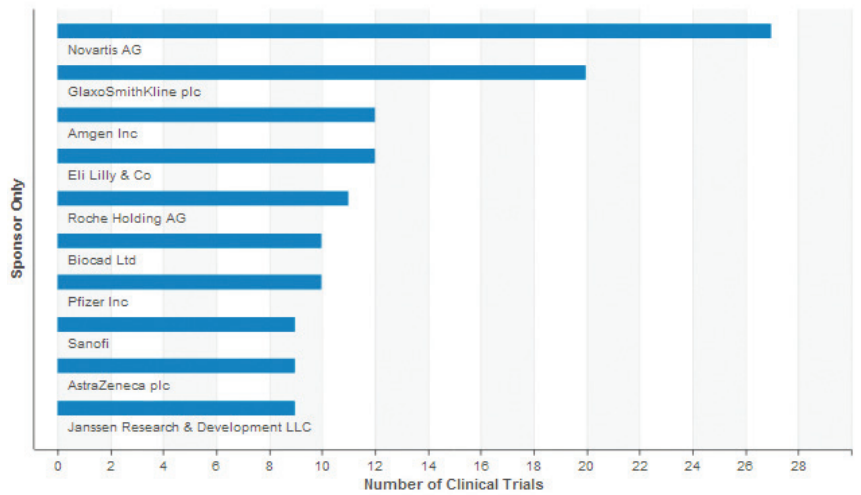


FIG 3B. NUMBER OF CLINICAL TRIALS INITIATED IN FOR PIONEER CONDITIONS IN RUSSIA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

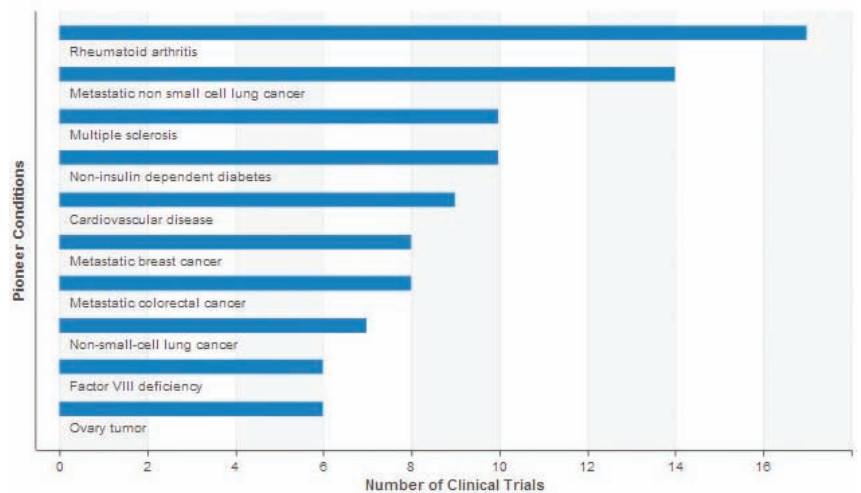


FIG 3C. NUMBER OF CLINICAL TRIALS INITIATED IN FOR PIONEER CONDITIONS IN RUSSIA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

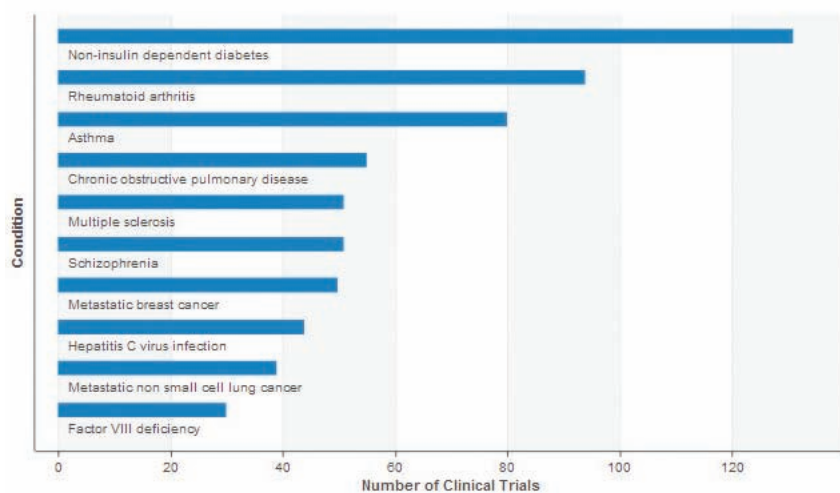


FIG 3D. NUMBER OF CLINICAL TRIALS INITIATED IN RUSSIA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

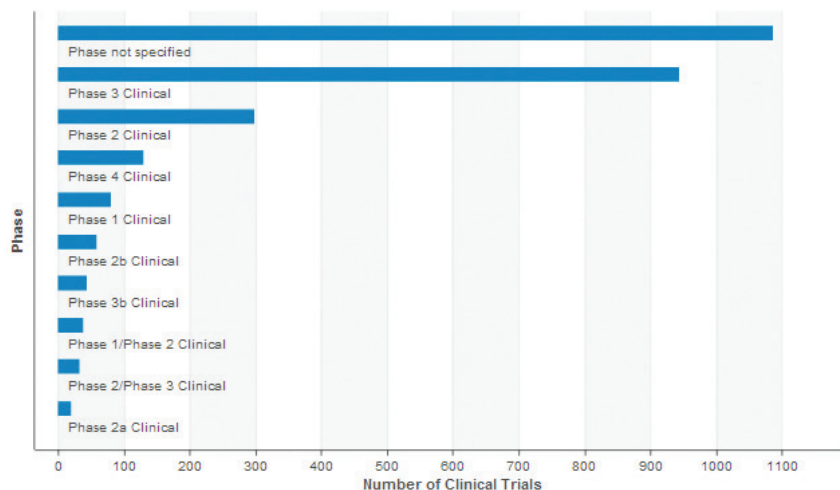


FIG 3E. NUMBER OF CLINICAL TRIALS INITIATED IN RUSSIA FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

INDIA

In 2017, India is predicted to move up to the 11th spot in global pharmaceutical spending⁽¹⁵⁾. Much like the other BRIC countries, India has a large, diverse, and mostly treatment-naïve patient population. Despite a historic increase in healthcare spending and implementation of a national system, a large percentage of the population still has limited access to adequate care. Although roughly 70 percent of the population lives in rural areas (27), quality medical facilities operating near Western standards are centralized in urban areas. Travel-intensive and poorly-equipped rural facilities result in an under-cared for patient population outside of the city centers. For more than basic care, Indian patients must rely on private healthcare, creating affordability issues and a health disparity between classes. A need for affordable and quality healthcare in the country, particularly for non-communicable diseases such as cancer and respiratory disorders, makes clinical trial recruitment fast and patient retention high. Though the doctor-to-patient ratio is lower than in Western countries and some other emerging markets, the Medical Council of India's accredited medical colleges are churning out a growing number of physicians each year. Primary health care centers are growing and quality is improving as good clinical practice is encouraged. Most of big pharma, as well as the world's largest CROs are present and accounted for. Cost-savings, if one can navigate the increasingly complex approval process, is upwards of 50 to 60 percent as compared to trials in the U.S.⁽²³⁾.

The Central Drugs Standard Control Organization (CDSCO) is the national regulatory agency for India and functions similar to the FDA and EMA. The head of the organization, the drug controller general of India, is tasked with pharmaceutical and medical device control and it is CDSCO who is responsible for approving clinical trial conduct in the country. CDSCO receives reviews of clinical trial applications from ethics committees, the Indian Council of Medical Research, the newly enacted New Drug Advisory Committees, and Medical Device Advisory Committees who operate as specialty review boards. The national Institutional Ethics Committee (IEC) or independent ethics committees review ethical content in clinical trial applications and continuously monitor the trial once it has begun. Although applications can be

submitted in parallel to CDSCO and IEC, the trial may only begin once approval is granted from both. This often results in a sequential process, lengthening timelines. The average time from application to approval in India is six months.

Much like in Russia, the Indian regulatory body is enacting changes faster than foreign pharmaceutical companies can keep up. Guidelines for audio-video recording of informed consent have been drafted, trial registration has been mandated, a call for compulsory accreditation of independent ethics committees has been answered, panels of experts for clinical trial application approval and serious adverse events reviews have been compiled, GCP-compliance is being ensured by CDSCO's new clinical trial inspection program, and safety update reports are required to be submitted every six months during the trial. This rapidly changing regulatory landscape is coupled with several losses in big pharma patent protection. Novartis, Roche, Merck, Gilead, and Pfizer have all lost patent cases in the country.

Since 2010, the initiation of clinical trials in India has declined sharply (Fig 1A). Sponsors such as Eli Lilly, AstraZeneca, Pfizer, and GSK have either pulled back or out completely, waiting for the regulatory landscape to stabilize. Trial subject deaths due to adverse events have plagued the country's clinical climate, and trust in Indian data is wavering. Biogen Idec suspended several of their trials for six months waiting to see how regulatory changes would impact them (16). Novartis, however, remains active amongst the ever-increasing local presence (Fig 4A). Novartis and Pfizer lead the number of trials investigating pioneer conditions, topping a combination of domestic sponsors and big pharma (Fig 4B). Conditions have been diverse (Fig 4C).

Late-stage trials are the most prevalent in India, with top therapeutic areas mimicking the global trend: diabetes, pulmonary diseases, and rheumatoid arthritis. Initiation of phase I and II trials have been steadily declining but showed a slight upward swing in 2013.

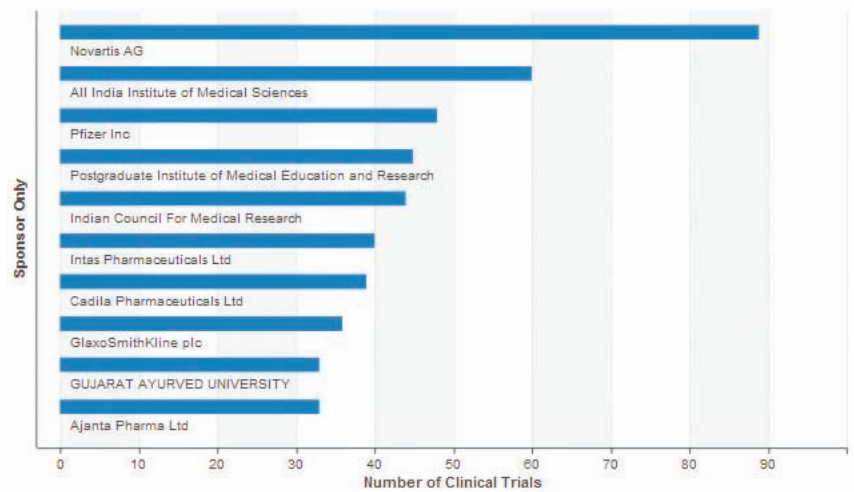


FIG 4A. NUMBER OF CLINICAL TRIALS INITIATED IN INDIA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

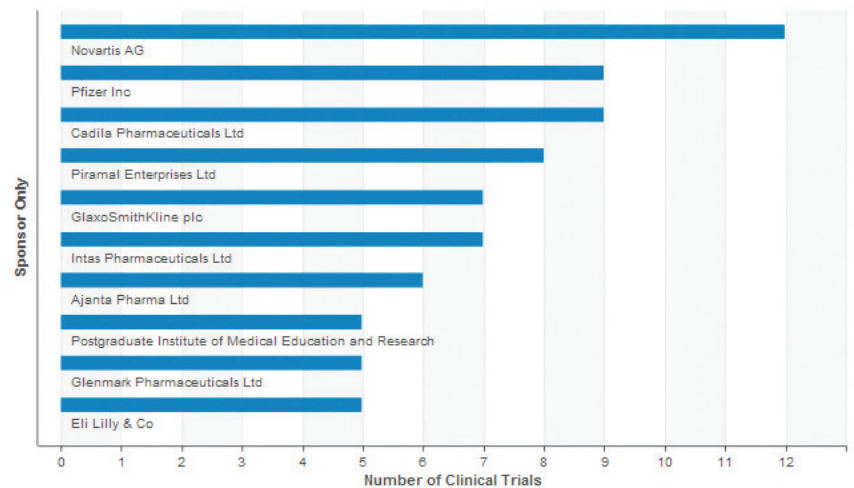


FIG 4B. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN INDIA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

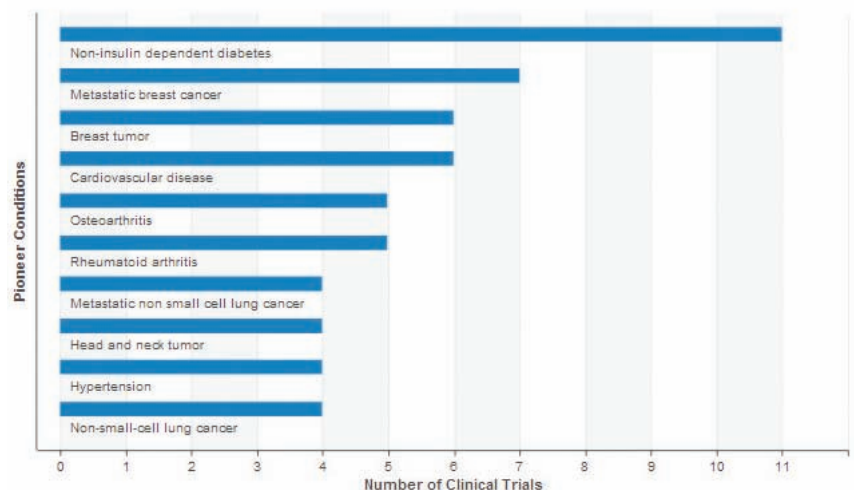


FIG 4C. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN INDIA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

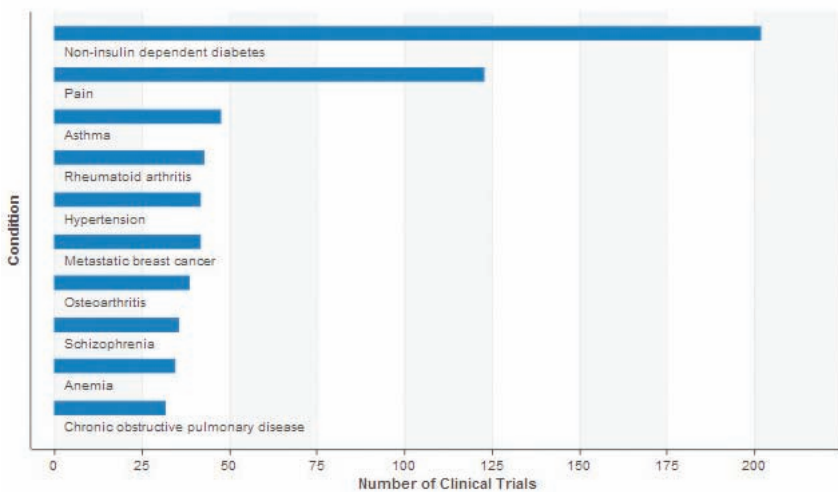


FIG 4D. NUMBER OF CLINICAL TRIALS INITIATED IN INDIA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

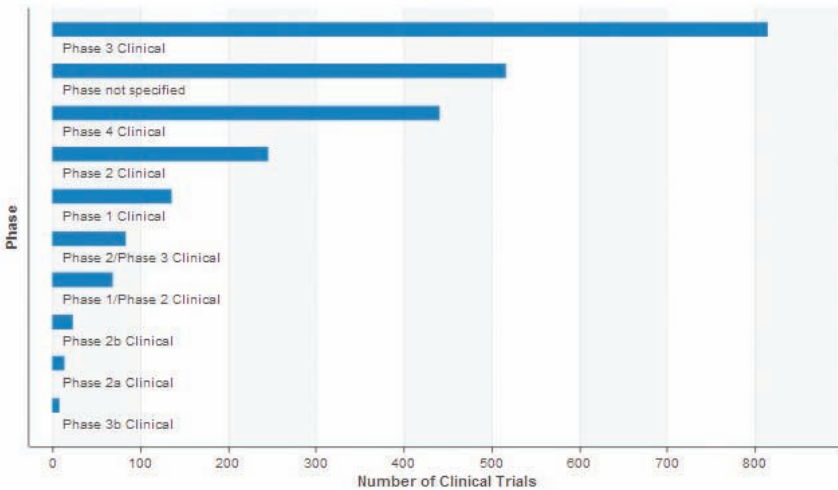


FIG 4E. NUMBER OF CLINICAL TRIALS INITIATED IN INDIA FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

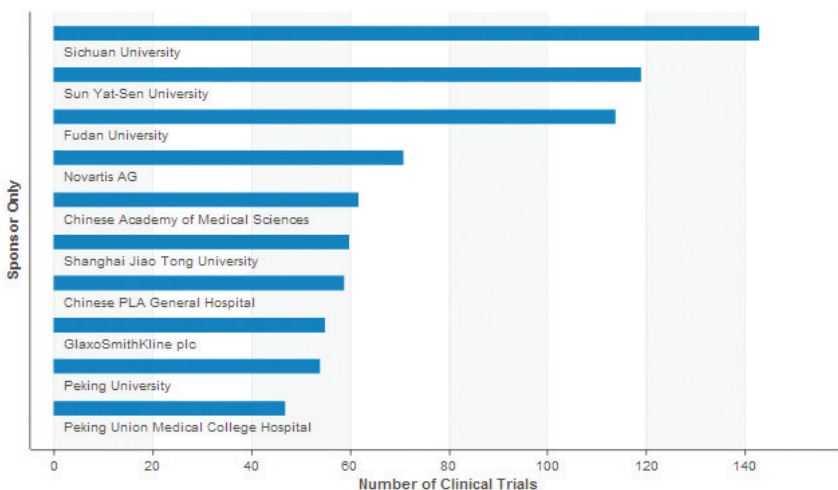


FIG 5A. NUMBER OF CLINICAL TRIALS INITIATED IN CHINA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

CHINA

If forecasts are correct, China will become the second largest pharmaceutical market in the world in 2017, overtaking Japan⁽¹⁵⁾. With an annual increase in the number of clinical trials conducted and big name sponsors outsourcing clinical trials to the country, China is expected to experience tremendous growth in drug development and research. Showcasing a large and aging population, increased R&D funding, improved regulatory control, and a rapid proliferation of health care professionals and research centers, the country is attracting sponsors looking to cut trial costs without sacrificing quality. In fact, China is the only BRIC country seeing an increase in the amount of clinical trials they are initiating every year. Recent developments in partnerships include AstraZeneca's with Beijing's premier clinical research laboratory, Pharmaron. Increased presence in the country is being accomplished by laying down an extensive network of on-ground expertise with CROs and is growing with entities like Novartis, Quintiles, Parexel, Covance's central laboratory, and Catalant's recently opened clinical trial supply facility in Shanghai.

In a revitalization effort, the regulatory body of China rebranded itself as the China Food and Drug Administration (CFDA) in 2013. The CFDA operates much like the FDA and tasks the Center for Drug Evaluation (CDE) with clinical trial application reviews. Approval in China is a lengthy and complicated process, with rigorous requirements necessary for the full dossier that is required of sponsors. Although working closely with the CFDA and CDE during the review process can efficiently move it forward, delays remain the biggest bottleneck to initiating clinical trials in China. Average approval timelines can range anywhere from six to 12 months. Clinical sites must be accredited by the CFDA and inspections may occur at any time during or after the trial has completed. GCP compliance is necessary and ethics committees at each site conduct ethical reviews of the trial protocol and implementation.

Despite an incomparable steady increase in clinical trial initiation in China over the past five years (Fig 1A), foreign sponsors face several issues that limit their cost savings in the drug development process. Regulatory red tape continues to become more complex as reform is underway. Genzyme has commented that the approval process for foreign sponsors conducting large, global trials

can take greater than one year in the country. Exporting biological samples is another issue altogether, requiring approval from the CFDA during which time the trial's data is unlocked, sometimes for up to a year. There are strict investigative drug importation policies requiring that three lots of the final drug be submitted for testing along with supporting data before the trial can be approved. Full disclosure of manufacturing processes and procedures must accompany the drug, causing data protection doubt with sponsors. A boom of central laboratories and manufacturers, however, are easing this pressure.

Local sponsors have continued their strong presence amongst the top companies initiating trials in China, with Novartis maintaining a spot through the past five years (Fig 5A). Pioneer conditions have largely been in oncology and investigated through domestic trials, with pioneer trials by Novartis and Bayer (Fig 5B & 5C).

Phase I trials must be performed in China with Chinese patients for all new drugs not already registered in another country. Due to the high incidence of local sponsors, however, early-stage trials are relatively elevated compared to other BRIC countries (Fig 5E). Phase III trials are being initiated in oncology and pulmonology in numbers close to those of early-stage trials, which focus mainly on oncology.

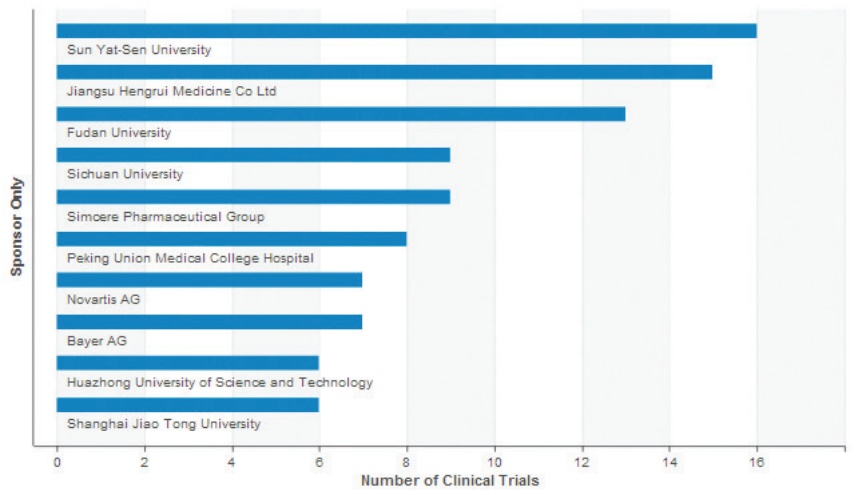


FIG 5B. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN CHINA FROM 2009-2013 BY SPONSOR (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

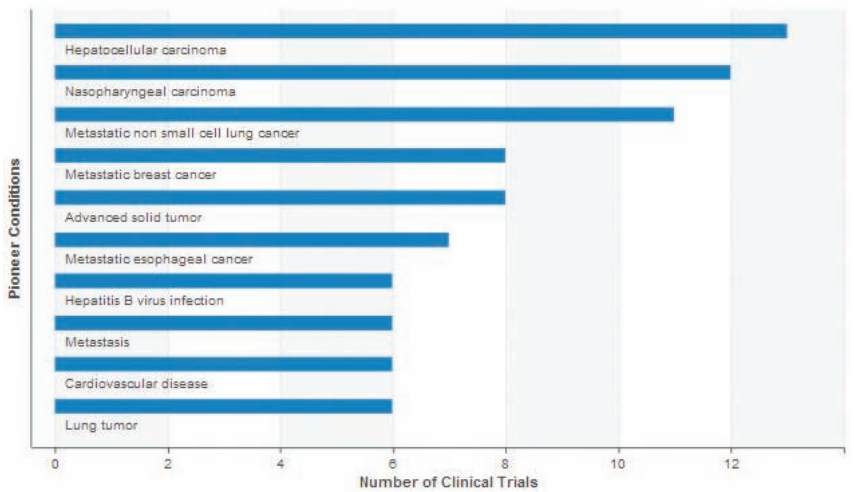


FIG 5C. NUMBER OF CLINICAL TRIALS INITIATED FOR PIONEER CONDITIONS IN CHINA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

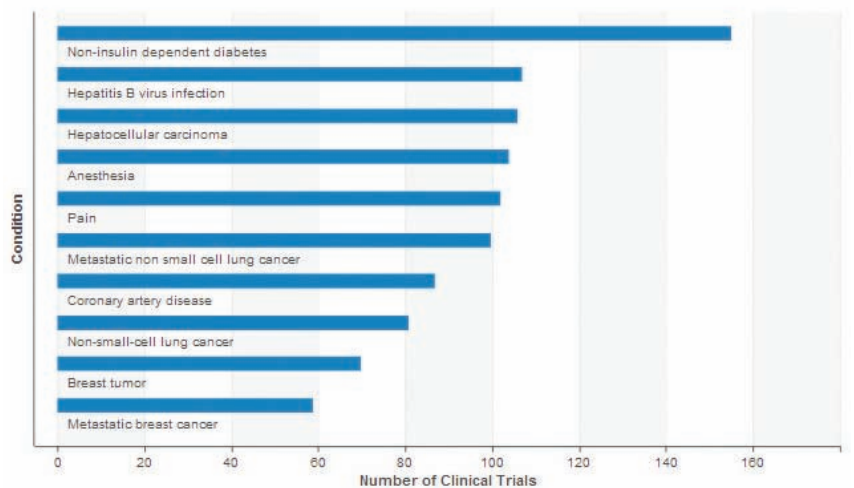


FIG 5D. NUMBER OF CLINICAL TRIALS INITIATED IN CHINA FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

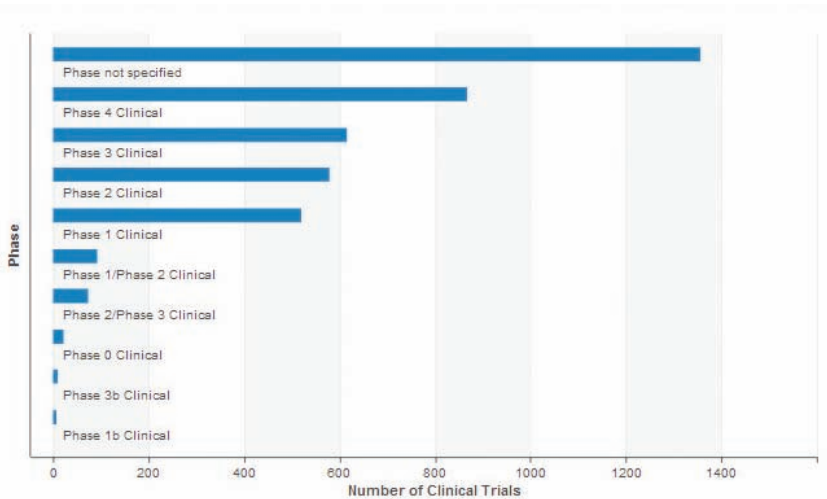


FIG 5E. NUMBER OF CLINICAL TRIALS INITIATED IN CHINA FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

COMPANY SPOTLIGHTS

It is clear that sponsors have been hesitant in initiating large-scale, global trials in BRIC countries as of late, presumably deeming the risks to outweigh the benefits. With this pull back, however, greater opportunity arises with widely accessible sites and available investigators, untapped patient pools and therapeutic areas, and a generous cost savings if the sponsor can deftly navigate the regulations. There are a few companies who have invested in BRIC and are continuing their rate of success even through the tumultuous times. The question remains, how?

NOVARTIS

Novartis International AG is the second highest ranking pharmaceutical company in the world. Having brought multiple blockbusters to market and conducting over 2,500 global trials since its inception, the company is no stranger to regulation adaptability. Their continued presence in BRIC despite dramatically falling trial numbers attests to that. At the Global Clinical Trials conference in 2013, Novartis remarked that big pharma generally has fewer issues than smaller companies. This is because Novartis maintains what they call an “on-the-ground” presence with local offices and pharmaceutical research centers in each market. This reduces reliance on CROs, which increases quality and decreases liability. It also maintains a direct pathway from the sponsor to the local regulating government agencies, easing the clinical trial application and drug importation processes⁽¹⁶⁾. Novartis has pharmaceutical development centers in Hyderabad, India and in Chanshu and Shanghai in China. Local pharmaceutical offices are located in multiple cities in all of the BRIC countries. Although having lost patent protection for Glivec in India in April 2013, initiation of trials in the country has remained relatively stable. Their presence in all the BRIC countries has met with little variation over the past five years, seeing only a distinct drop in China. Novartis’ Alcon met with bribery allegations in China in 2013, which may have contributed to this decline.

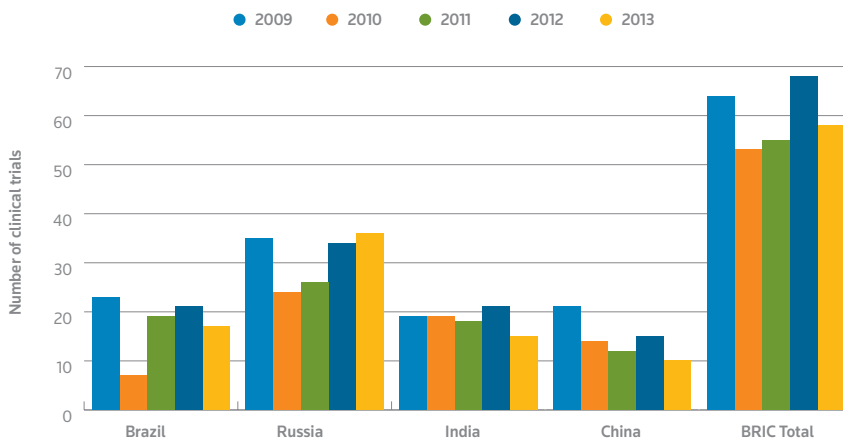


FIG 6A. NUMBER OF CLINICAL TRIALS INITIATED BY NOVARTIS IN BRIC COUNTRIES FROM 2009-2013 (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

NOVO NORDISK

Although technically considered big pharma, Novo Nordisk is often absent from discussions about the big players in drug development. Prolific in diabetes, hemophilia, and inflammation, the protein-based company has been increasing their presence globally. Novo Nordisk maintains one local office in each BRIC country, R&D sites in Beijing and Bangalore, as well as production plants in Brazil and China. They are currently investing in a modern insulin plant in the Kaluga region of Russia. The company is active in the local communities as well, initiating arts programs (Novo Arts program in Brazil) and drawing attention to diseases through charitable events.

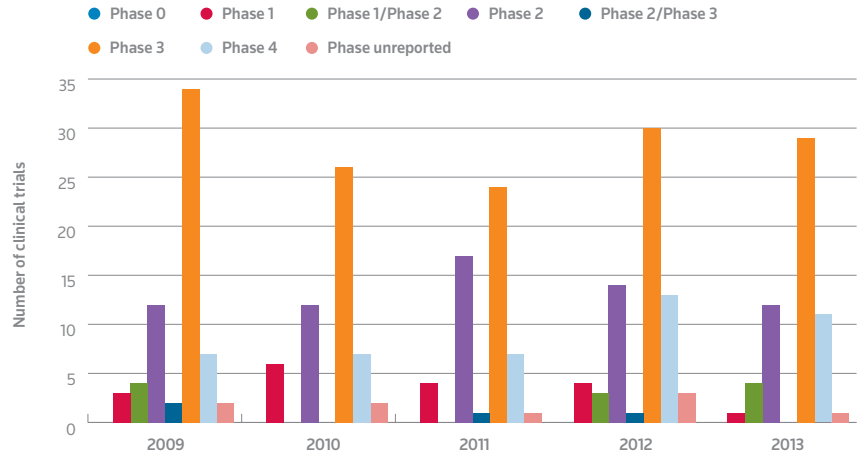


FIG 6B. NUMBER OF CLINICAL TRIALS INITIATED BY NOVARTIS IN BRIC COUNTRIES FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

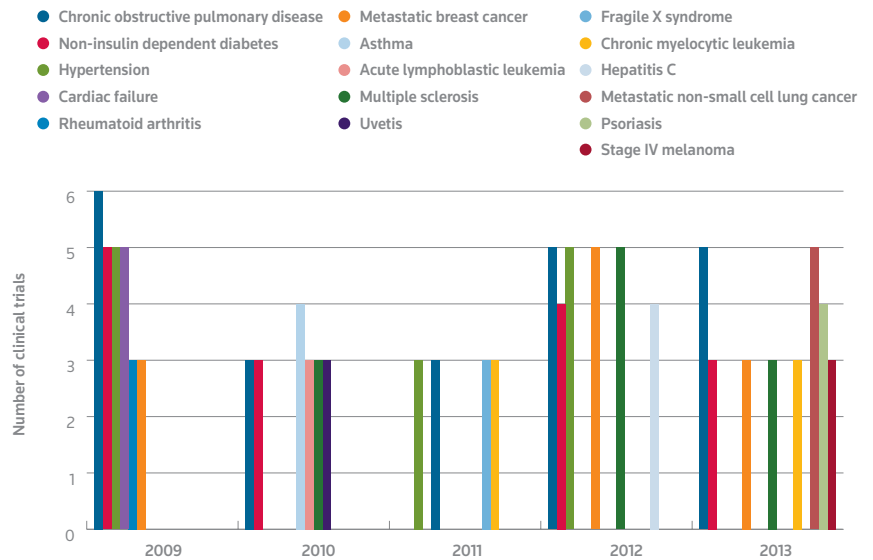


FIG 6C. NUMBER OF CLINICAL TRIALS INITIATED BY NOVARTIS IN BRIC COUNTRIES FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

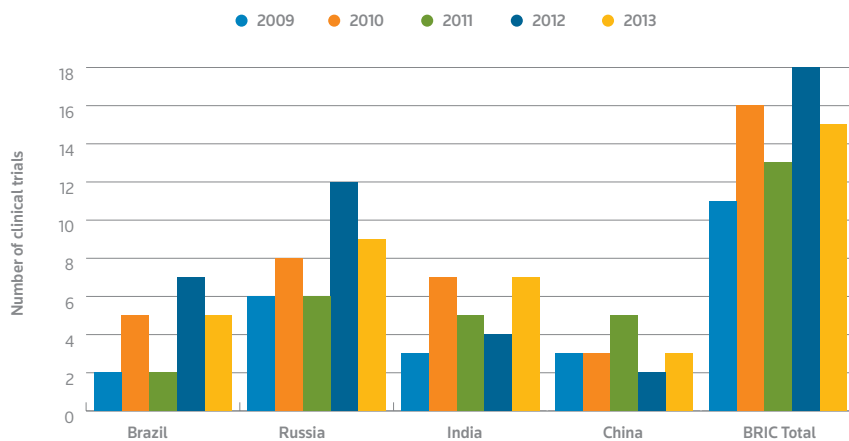


FIG 7A. NUMBER OF CLINICAL TRIALS INITIATED BY NOVO NORDISK IN BRIC COUNTRIES FROM 2009-2013 (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

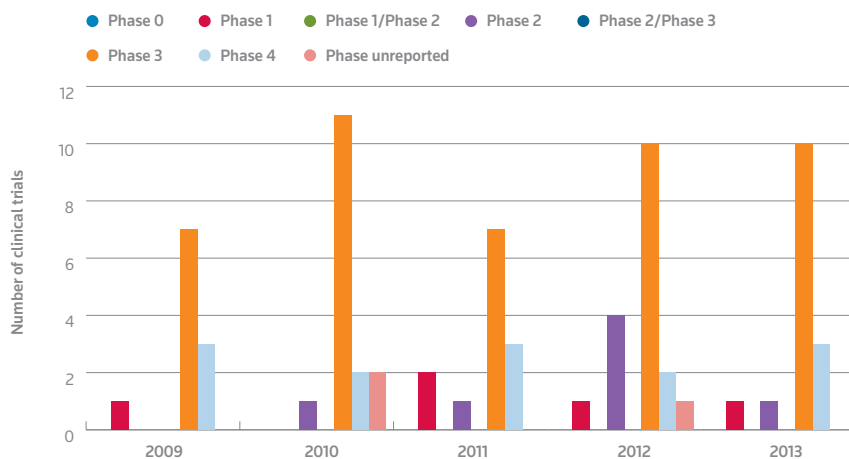


FIG 7B. NUMBER OF CLINICAL TRIALS INITIATED BY NOVO NORDISK IN BRIC COUNTRIES FROM 2009-2013 BY PHASE (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

BIOCAD

Biocad is a small Russian pharmaceutical company that has been exhibiting a steadily increasing presence in Brazil and India. They have initiated clinical trials of rituximab, a biosimilar, in India and Russia, and are navigating even more complex regulations and/or unprecedented pathways than new drugs require. Local offices in Brazil, India, and China afford them an “on-the-ground presence” for building regulatory agency relationships. Development for a new Biocad plant in Parana, Brazil for the production of biosimilars trastuzumab and rituximab is underway.

LESSONS

Despite the attractiveness of fast recruitment and cost-effective trials, there are many issues unique to the BRIC markets that can delay trials and drive costs upwards. Local needs, regulatory hoops, trial drug delay in customs, manufacturing quality or biodegradation (uncontrolled climate during shipping), lack of globalized GCP and Good Clinical Laboratory Practice (GCLP) standards, high turnover rate of CROs (40 percent according to Biogen Idec), and a disconnection of data between sites and sponsors and/or CROs⁽¹⁶⁾ are all caveats that must be overcome. The spotlighted sponsors above have navigated the red tape via many avenues, chiefly by partnering or maintaining a local presence. The methods discussed can be said for all those wishing to conduct successful clinical trials in BRIC countries.

LOCAL PRESENCE

Successful sponsors have repeatedly advocated that maintaining local units and/or partnering with CROs, as well as working with local consultants, is necessary for the swiftest approval timeline. Although big pharma has spread through most emerging markets, smaller companies must partner with those who have feet on the ground in local areas to avoid regulatory tangles. This agrees with results from Pharma IQ's most recent survey regarding conducting clinical trials in BRIC countries. In choosing a CRO, the following criteria are the most crucial (in order of importance): local expertise, global reputation, specialization in a therapeutic area, an existing relationship, size of CRO (20). CRO giants Quintiles, Parexel, INC Research, and Covance all operate locally in the BRIC countries.

TECHNOLOGY

Although technology is prevalent throughout the healthcare field, not all sites have implemented the most efficient clinical trial data capture systems. Online training and a global electronic data capture system can lead to greater GCP compliance and the ability to track clinical trial progression in real time. TransCelerate BioPharma, an R&D focused organization of big pharma, aims to harmonize standards industry-wide for risk-based monitoring. A shared investigator portal, site qualification and training, as well as data standards and comparator drugs, are all foci of the new initiative. The FDA has not approved TransCelerate's initial risk-based monitoring plan, however it is still at the forefront of their mission. Industry experts indicate that the future of data management will showcase a central data capturing tool that is linked through a Clinical Trial Management System to allow access by CROs. This will be supplemented with in-house clinical research associates CRAs to monitor the central information and data privacy officers for patient information protection. Additionally, it will enable companies to take electronic data capture snapshots and look at the performance per site in real time as well as increase transparency and communication across the industry. Online training on protocols, GCP, and good clinical laboratory practice is being provided by sponsors and CROs, and in some cases, free of charge to industry and regulatory bodies. They include mechanisms to ensure understanding⁽¹⁶⁾.

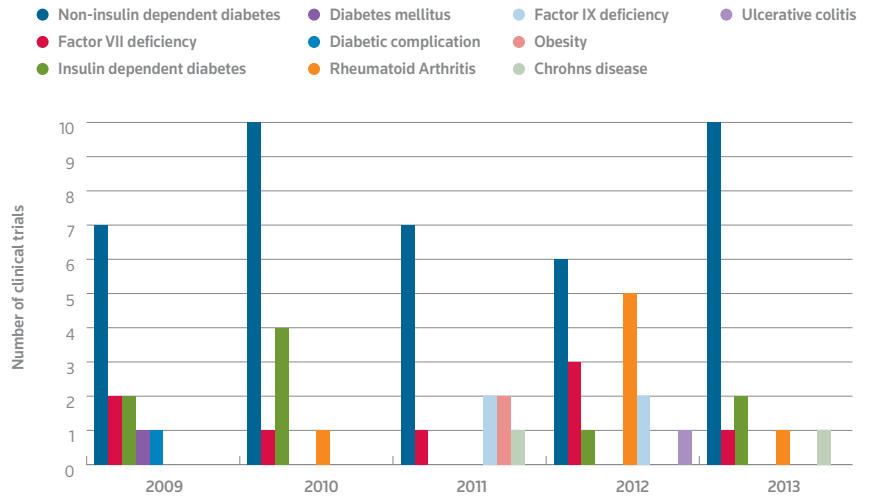


FIG 7C. NUMBER OF CLINICAL TRIALS INITIATED BY NOVO NORDISK IN BRIC COUNTRIES FROM 2009-2013 BY CONDITION (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

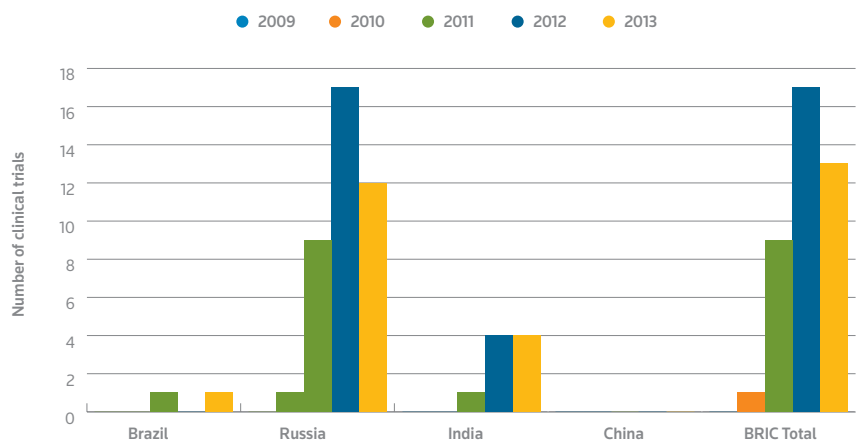


FIG 8. NUMBER OF CLINICAL TRIALS INITIATED BY BIOCAD IN BRIC COUNTRIES FROM 2009-2013 (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

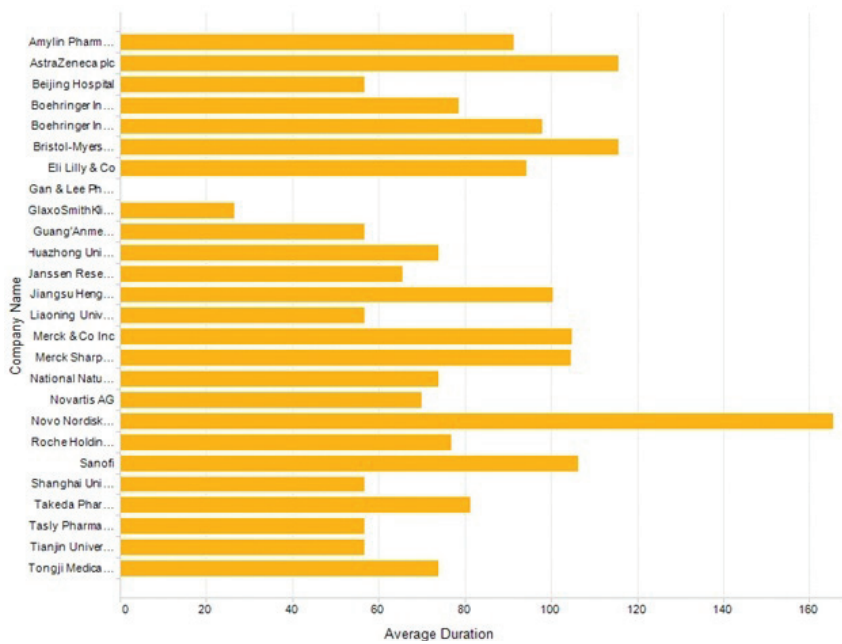


FIG 9A. AVERAGE DURATION OF PHASE III CLINICAL TRIALS INITIATED IN NON-INSULIN DEPENDENT DIABETES IN CHINA FROM 2009-2013 (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

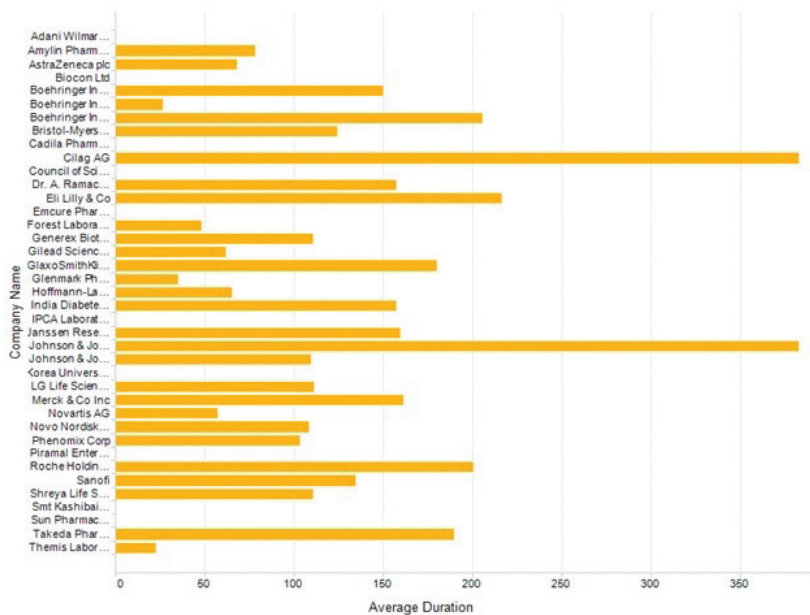


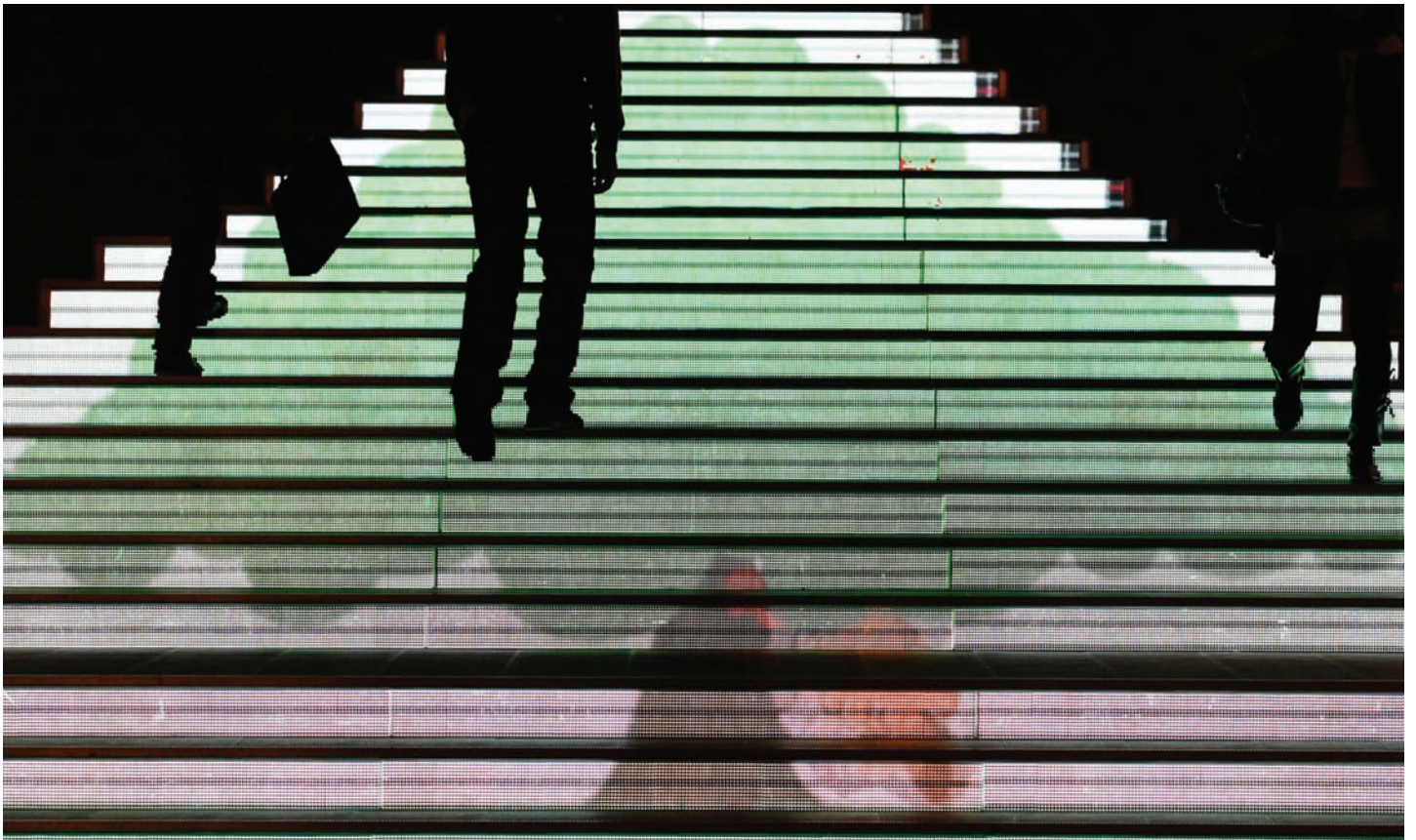
FIG 9B. AVERAGE DURATION OF PHASE III CLINICAL TRIALS INITIATED IN NON-INSULIN DEPENDENT DIABETES IN INDIA FROM 2009-2013 (CORTELLIS CLINICAL TRIALS INTELLIGENCE, FEBRUARY 18, 2014)

CONCLUSION

While Brazil and Russia have been maintaining a slow decline in trial initiation over the past five years, it is clear that China and India have divergent patterns. This pattern continues when looking at phase III trial durations in the most prevalent condition studied: non-insulin dependent diabetes (Fig 9A & 9B). While India's average trial duration is certainly shorter than that of China, trials in China are increasing year after year. Could it be that there are reasons beyond trial initiation issues that are giving sponsors second thought about India? Or perhaps it is merely driven by varying treatment durations associated with each country's patient population and corresponding conditions. One thing is for sure, the BRIC clinical trial climate is changing. While some sponsors are beginning to explore other emerging markets, there are others who have decided to stay and invest in BRIC. Those that believe that despite the rapidly changing regulatory requirements, corruption, and patent protection losses, BRIC countries remain cost-effective and timely if a sponsor can navigate the red tape. By increasing local presence in these countries and building a strong relationship with regulatory bodies, local CROs and consultants, sites and investigators, and the community, it is possible to reap the benefits of fast recruitment and quality data that these markets afford.

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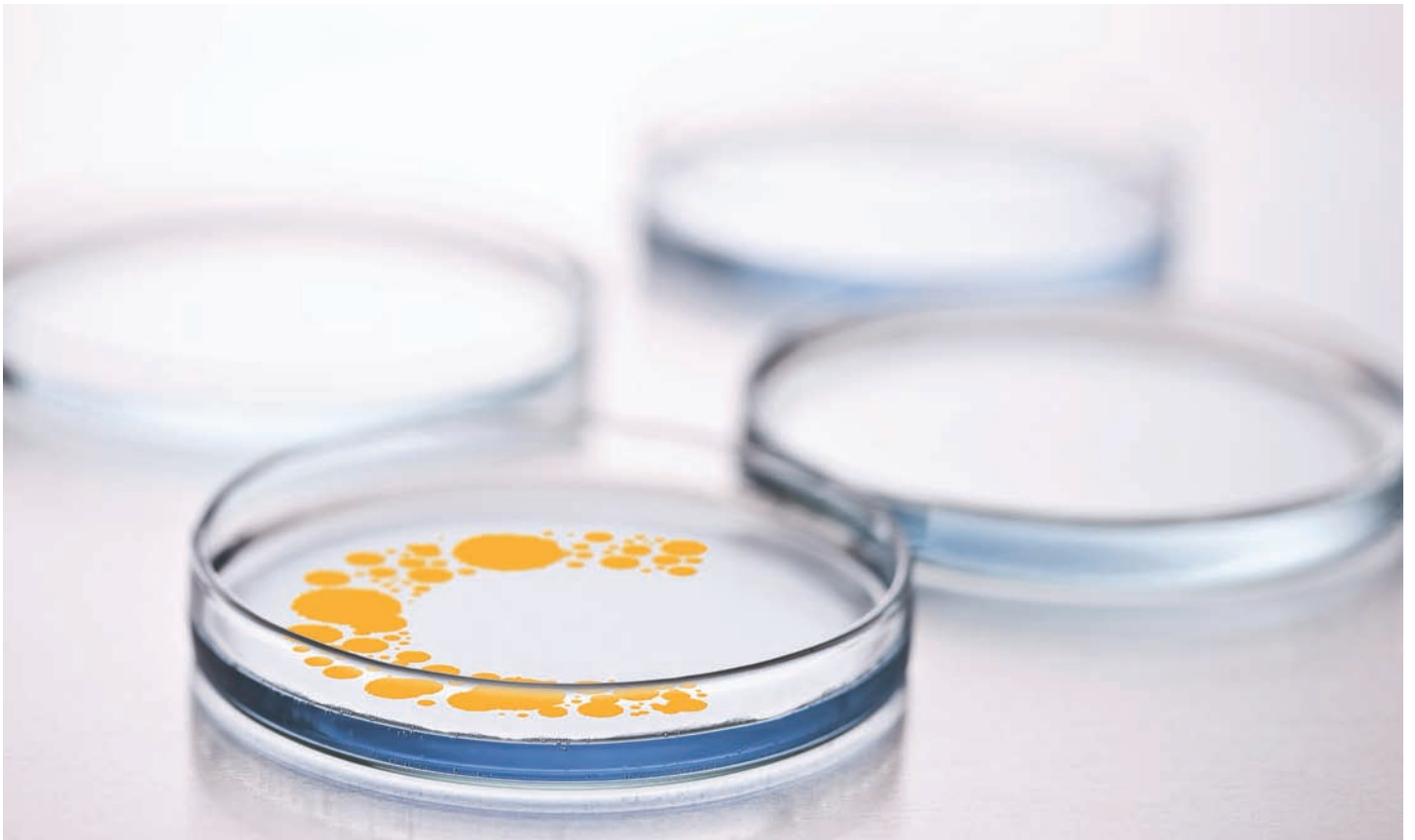
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