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# QUANTIFYING THE ECONOMIC GAINS OF STRENGTHENING INDIA'S CLINICAL RESEARCH POLICY ENVIRONMENT

Study and Key Findings – September 2015

This report was commissioned by the Pharmaceutical Research and Manufacturers of America (PhRMA). The views represented here are those of the authors only.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| BCI | The Biopharmaceutical Competitiveness & Investment Survey |
| BRICs | Brazil, Russia, India and China |
| CTs | Clinical trials |
| CROs | Clinical Research Organizations |
| FDIs | Foreign Direct Investments |
| GCP | Good Clinical Practice |
| GDP | Gross Domestic Product |
| GIPC Index | The US Chamber Global Intellectual Property Center's International Intellectual Property Index (an established international best practice standard for measuring national IP rights) |
| GMP | Good Manufacturing Practice |
| IMF | International Monetary Fund |
| IP | Intellectual Property |
| OECD | Organization for Economic Co-operation and Development |
| PMR Index | The OECD's Product Market Regulation Index (an established international benchmark for measuring national regulatory environments) |
| PPP | Purchasing Power Parity |
| R&D | Research & Development |
| SMOs | Site Manager Organizations |
| TRIPS | WTO Agreement Trade-Related Aspects of Intellectual Property Rights |

# EXECUTIVE SUMMARY

Clinical trials have crucial public health, social and economic benefits that align with many strategic policy objectives of governments today – from enabling local access to needed cutting edge treatments and building domestic biopharmaceutical sectors to supporting containment of health care and pharmaceutical costs and driving wider economic gains.

Coming from a relatively low starting point in its current level of clinical trial activity – by some estimates, one of the lowest rates of annual clinical trials globally – India is a country that could benefit significantly from greater clinical trial activity.

Why does such a gap exist between India's potential in clinical trial activity and actual current levels? And how exactly might India benefit from addressing the factors behind this gap?

One key component for enhancing a given economy's clinical trial activity is the clinical research policy environment. The policy trajectory in a given economy can have a real and significant impact on the investment decisions and recommendations that multinational research-based biopharmaceutical companies make.[1] While elements such as overall costs and market characteristics play a part in investment considerations, other factors, such as the regulatory and legal frameworks governing the registration and conducting of clinical trials as well as available healthcare resources, also have a strong impact on the ability and willingness of companies to invest in clinical research in a given economy.[2] Indeed, evidence suggests that economies with supportive policy environments tend to experience much higher rates – according to some estimates, on average ten times more – clinical trial activity and associated economic gains than those with policy environments lacking in these key aspects.[3]

This study aims to analyze India's clinical research policy environment in relation to international best practices, and in so doing identify which policy improvements might support greater clinical trial activity in the country and quantify the resulting wider, positive economic effects. For this purpose, a new model is created that:

a) measures the level of clinical trials currently taking place in India as well as its clinical research policy environment compared to other leading markets;

b) statistically gauges which aspects of the policy environment matter most for clinical trial intensity; and finally,

c) computes the effects of policy reform on investment in clinical research based on previous studies and international experience, providing scenario analysis of the impact of key policy improvements in India on its number of clinical trials, FDI and additional externalities.

## Key findings

The study firstly shows that key factors in today's low clinical trial intensity in India relative to other leading markets include existing policy challenges in the country related to clinical research, particularly in relation to the regulatory system, legal framework and resources enabling the capacity for conducting and controlling clinical research.

Indeed, as it stands now the regulatory system in India vis-à-vis clinical research faces major challenges, not least important gaps in predictability and transparency in the criteria and processes governing clinical research outlined in the Drugs and Cosmetics Act, and continuing to exist in amendments to this legislation available earlier in 2015. These include clinical trial approval protocols as well as procedures for addressing trial-related injuries or adverse effects.

Moreover, a high level of uncertainty and antagonism exists towards certain aspects of the legal framework. India's patentability requirements remain outside established international best practices; in the past 3-4 years India has discussed

the use of compulsory licensing, and in one instance issued a compulsory license, on bases outside its obligation under the TRIPS Agreement; and there is a lack of specific biopharmaceutical IP rights such as regulatory data protection. Research-based companies in India also experience drawn-out litigation and difficulties securing meaningful and timely remedies for infringement.

In addition, the Indian drug regulatory agency, at both the central and state levels, lacks adequate resources for needed capacity building, funding and infrastructure in order to ensure a high quality and efficient clinical research system in India.

As a result of these and other policy issues affecting clinical research India tends to place in the **bottom quartile** in global benchmarks related to the clinical research policy environment, such as the 2015 Biopharmaceutical Competitiveness & Investment (BCI) Survey, the OECD's 2013 Product Market Regulation (PMR) Index and the 2015 GIPC International Intellectual Property Index.

Yet at the same time, numerous empirical studies suggest that improvements to the policy environment and addressing outstanding concerns could have a significant impact on attracting and securing greater investment and associated economic gains. This study has shown that even small improvements to the Indian clinical research policy environment, for instance in the areas outlined above, could result in considerable gains across the Indian public health system and economy.

The two figures on the next page summarize the key investment and economic gains estimated to arise from policy improvements that would allow India to reach roughly the median percentile (40th to 60th) on representative global benchmarks including those mentioned above. The range of expected gains are estimated based on the modeling in key studies such as from the OECD, Nicoletti et al. (2003) and Cavazos et al. (2010) which find that a 1% policy change leads to a 1.2% and 2.8% increase in FDI, respectively.

In other words an improvement in India's clinical research policy environment that roughly equals the median level of international best practices as quantified in this study could **increase India's number of new clinical trials per year to above 800 and add over 600 million dollars in direct monetary transfers and indirect economic gains**. This may be regarded as a conservative estimate; it is possible India could experience even higher levels of investment and economic gains.

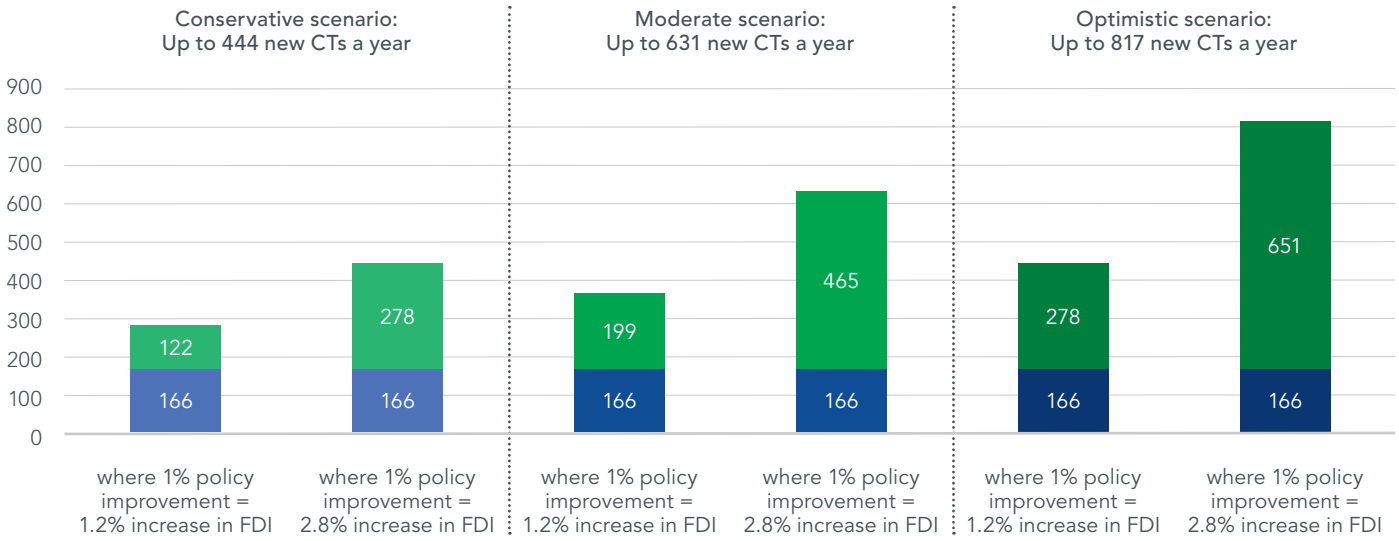
In order for India to secure the full level of investment and monetary and economic gains identified in this study and modeling, the following table outlines the most urgent policy elements needing to be addressed in India within the area of clinical research.

## Current improvements required in India's clinical research policy environment

| Policy area | Policy improvements needed |
|---|---|
| Regulatory framework | • In the Drugs and Cosmetics (Amendment) Bill 2015 and amendments to the Drugs and Cosmetics Rules, 1945:<br>– Include a clear definition and protocol surrounding trial-related injuries and liability in line with international best practices<br>– Clarify procedures for clinical trial approval revocation and suspension of the Ethics Committee, and introduce adequate recourse mechanisms<br>– Provide for a transparent and predictable site inspection process<br>• Ensure the above is also consistently applied in practice |
| Legal framework | • Strengthen the patent system by removing barriers to entry and enhancing predictability<br>• Harmonize the Indian patent system with international best practices<br>• Introduce regulatory data protection |
| Health care resources | • Increase targeted funding and resources to the Indian drug regulatory agency at both the central and state levels aimed at capacity building and greater efficiency |

Source: Pugatch Consilium, PhRMA, 2015

## Estimated gains to clinical trial activity in a given year, based on three scenarios within a median level of policy reform

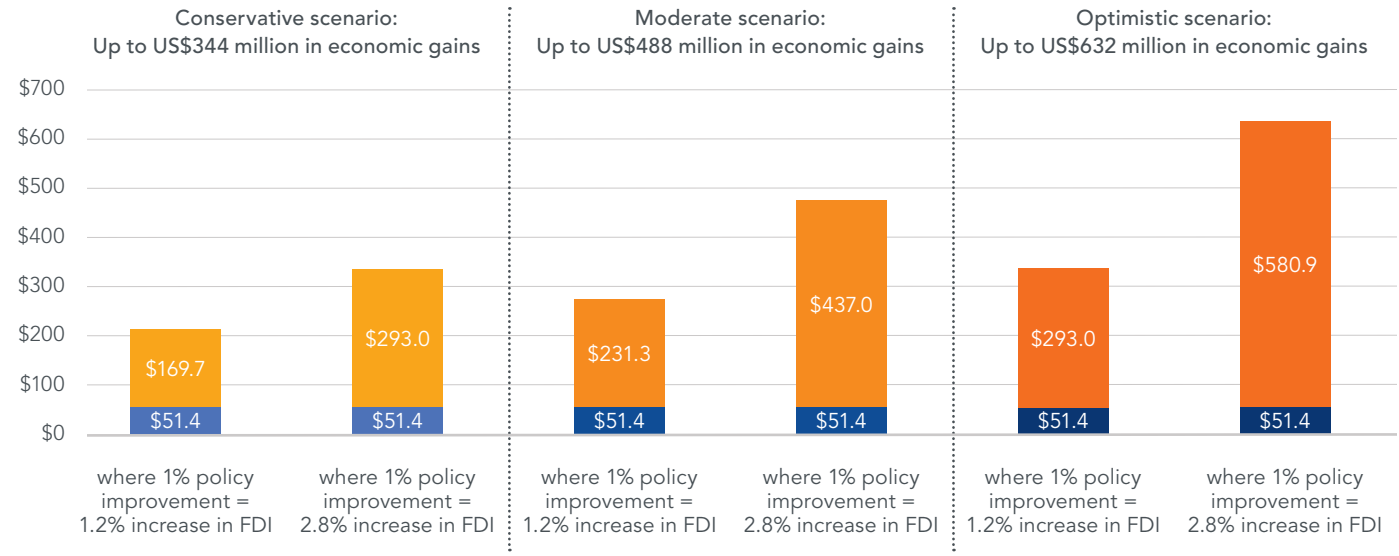



Baseline level of clinical trial activity (in terms of new clinical trials in 2014)

Estimated maximum level of new clinical trial activity following policy reform

Source: Pugatch Consilium; Note: the 3 scenarios roughly equate to the median level of international best practices identified in key relevant global benchmarks (e.g. OECD, 2013; GIPC, 2015); the methodology used to calculate the baseline figure of 166 clinical trials in India in 2014 is outlined in detail in the methodology section

## Estimated economic gains in a given year associated with clinical trial activity, based on three scenarios of policy reform




Baseline level of economic gains from clinical trials in a given year (based on latest available data)

Estimated minimum level of economic gains from clinical trials following policy reform

Source: Pugatch Consilium; Note: the 3 scenarios roughly equate to the median level of international best practices identified in key relevant global benchmarks (e.g. OECD, 2013; GIPC, 2015)

# 1 INTRODUCTION

Clinical trials, or research studies examining the effect of interventions such as medicines on human volunteers, have crucial public health, social and economic benefits that align with many strategic policy objectives of governments today. These include enabling development and local access to needed cutting edge treatments, building domestic biopharmaceutical sectors, supporting containment of health care and pharmaceutical costs and driving wider economic gains.

India, in particular, is a country that stands to benefit significantly from greater clinical trial activity. Despite it being a large and low-cost market with a strong foundation in manufacturing and contract research, India nevertheless currently hosts only 0.14 clinical trials per million population, which is among the lowest rates globally.[4] Why does such a gap exist between India's potential in clinical trial activity and actual current levels? And, how exactly might India benefit from addressing the factors behind this gap?

The purpose of this paper is two-fold: 1) to identify policy factors in India's biopharmaceutical R&D and clinical research environment that may be strengthened in order to enhance clinical trial activity taking place in the country; and, as importantly, 2) to understand and quantify the positive economic effects of these policy improvements.

For this purpose, a new model is created that:

a) measures the level of clinical trials currently taking place in India as well as its clinical research policy environment compared to other leading markets;

b) statistically gauges which aspects of the policy environment matter most for clinical trial intensity; and finally,

c) computes the effects of policy reform on investment in clinical research based on previous studies and international experience, providing scenario analysis of the impact of key policy improvements in India on its number of clinical trials, FDI and additional externalities.

In this light, this report does four things. First, it outlines the value of clinical trials across the economy (including the benefits for patients, physicians and scientists, health care institutions and the broader economy) and identifies certain key enabling factors for increasing a given economy's clinical trials intensity. Second, the report examines India's current clinical research environment in relation to these factors and based on different global benchmarks. Third, and perhaps most importantly, by constructing a computational model which quantifies the effect of improving an economy's clinical research policy environment on the level of investment and economic gains, the report considers what concrete gains India could expect to experience if it were to improve its policy environment in key areas. The final section summarizes the findings of the study and their implications for on-going policy discussions currently taking place in India.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# 2 THE ECONOMIC AND WELFARE BENEFITS OF CLINICAL RESEARCH AND KEY ENABLING FACTORS

Clinical trials represent one of the most important activities carried out by biopharmaceutical companies in different countries. They are fundamental components of the biopharmaceutical research and development process.

## 2.1 Clinical trials in the context of the biopharmaceutical R&D process

Conducting clinical trials is part of an extensive process for determining which compounds out of hundreds under investigation may be further developed and eventually brought to market, and in what manner. Clinical research enables companies and drug regulators to ensure that new drugs or new uses, forms or dosages of existing drugs will be safe and effective for use. It also often uncovers novel applications of medicines and medical devices or facilitates tailoring drugs to different populations.

Clinical trials are conducted within a highly controlled and studied environment where all aspects of a drug candidate are monitored, recorded and subject to high levels of scrutiny and evaluation. The process includes complying with a wide range of regulations governing international best practices related to the quality, safety and efficacy of drugs, for instance, Good Laboratory Practice guidelines on conducting toxicity studies, Good Manufacturing Practice and protecting the rights of patients through Good Clinical Practice.[5]

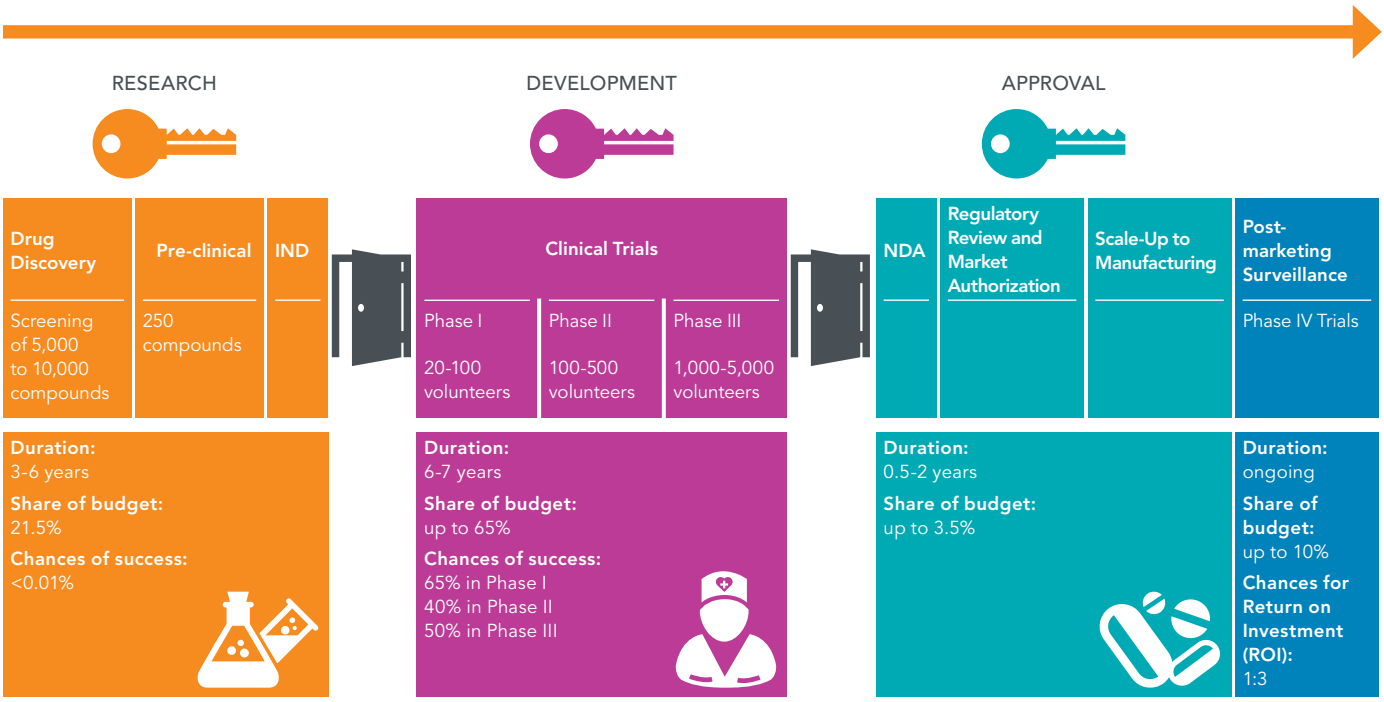
Figure 1 underscores the vital role played clinical trials in the biopharmaceutical R&D process.

FIGURE 1 The biopharmaceutical R&D process


Source: Pugatch Consilium, based on FDA (2014)[6]

Moreover, while the entire biopharmaceutical R&D process surrounding the creation of a new drug is a very involved and a financially risky process, with significant resources invested, clinical trials make up the most complex and riskiest portion. As Figure 2 suggests, the testing of drug candidates in human volunteers via clinical trials prior to market authorization,[7] which is divided into three main phases, represents an undertaking of 6-7 years per drug candidate, or between 55% and 75% of the total R&D process.[8] Various sources cite different figures for the length and cost of the clinical trials phase, ranging from $84.5 million to at least $1.17 million.[9] These numbers are continuously on the rise, and have doubled in the past decade.[10] Phase II trials represent one of the riskiest segments of the R&D process, involving a substantial investment with 100-500 volunteers per trial but only a 40% success rate.

FIGURE 2 Pharmaceutical R&D process timeline




Source: Pugatch Consilium; adapted from PhRMA[11] and Nature[12]

## 2.2 The value of clinical research as a type of biopharmaceutical investment

In this light, beyond enabling companies and drug regulators to ensure that new drugs will be safe and effective for use, clinical trials provide a wide number of economic and social benefits to patients, health systems and national economies.

First and foremost, clinical trials provide patients with access to innovative drugs, which may literally revolutionize existing treatments available domestically for prevalent diseases.[13] Access to these treatments may continue beyond the duration of the clinical trial.[14] Furthermore, participation in multinational, cutting-edge research helps ensure that clinical trials meet international standards of "Good Clinical Practice", and increases the quality and professional development of medical staff as well as researchers, scientists and clinical research organization (CRO) personnel, by exposing them to new techniques and treatment strategies. Moreover, clinical trials often involve improvements to infrastructure – hospitals, clinics and health technologies – local communities.[15]

In addition, conducting clinical trials in a given country involves financial flows to hospitals, CROs, site management organizations (SMOs), clinicians, patients, payers and government.[16] These transfers may take the form of, among other things:

- fees paid to institutions, physicians and patients for participating in clinical trials;
- improvements to infrastructure and technologies in local communities as well as capacity building within the local clinical research industry;
- savings on pharmaceutical and health spending, with the drug itself and associated tests and treatments often borne by the study's sponsor;
- tax contributions derived from revenue earned on clinical trials by sponsors in a given country; and
- long-term increase in employment and taxable revenue from growth of the local clinical research industry.[17]

Altogether, such financial transfers, whether direct or indirect, lead to considerable savings and economic benefits for a wide range of stakeholders. The exact distribution and amount accrued to different stakeholders from the total clinical research taking place in a given market will naturally vary case by case and by type of trial. Nevertheless, a meta-analysis of recent studies that break down costs of clinical trials by different components and actors[18] suggests that, on average, key stakeholders tend to benefit from the following portion of total annual monetary flows derived from clinical trials:

TABLE 1 Average share of clinical research-derived monetary transfers accrued by key stakeholders[19]

| Key stakeholder | % of total expenditure accrued to the stakeholder |
|---|---|
| Hospitals/clinics/institutions (including physicians' salaries) | 40% |
| CROs | 45% |
| Payers | 15% |
| Others (including patients) | 15% |

Source: Pugatch Consilium analysis, based on Sertkaya et al. (2014), Battelle (2015)

## 2.3 Key factors for enabling strong clinical trial activity

But how can a given economy increase its clinical trials intensity and experience the above discussed economic and welfare benefits? Which factors within the clinical research environment help increase a given economy's competitiveness in this field?

Conducting clinical research necessitates a supportive environment, with numerous factors needing to be in place in a market to grow local clinical research activity. By understanding which clinical research policies are effective and which are not countries can streamline policy measures aimed at enhancing investment in clinical research. Indeed, the biopharmaceutical innovation system is driven by several science and technology "push factors", including investment in biopharmaceutical R&D, a steady source of cutting edge advances in the life sciences and a sustained supply of physical and human resources available and utilized for biopharmaceutical innovation.[20]

With regards to clinical trials activity, a sizeable body of literature discusses which factors are most important for stimulating growth of investment in clinical trials in a given country. One recent study suggests that the strength of intellectual property protection can explain around 40% of clinical trial activity.[21] Other studies suggest that a range of other factors are also important, including clinical capacity and infrastructure, access to health care, quality of regulatory frameworks, market conditions and ability to recruit and retain volunteers.[22]

Based on an analysis of the range of factors empirically linked to clinical trial activity, this report identifies four major areas that are seen as important to sponsors when deciding where to locate clinical trials. These are: the regulatory environment; the IP/legal environment; healthcare resources; and market conditions. The following paragraphs outline how each area and various elements or factors within each area support clinical trial activity.

### The regulatory environment

The regulatory environment in a given economy plays an important role in shaping incentives for investment and establishing adequate levels of quality and safety for clinical trials and biomedical products. Inadequate or unpredictable approval standards that may enable the presence of substandard drugs or adverse reactions during the clinical trial process and beyond are more likely to discourage investment in that economy.[23] For instance, where a predictable and transparent framework for monitoring and controlling the conduct of clinical trials is absent and/or not consistently applied, clinical trial sponsors may find it difficult to ensure that the trials are conducted under strict safety protocols and adherence to international standards, such as the ICH's GCP and GMP standards. This is particularly challenging for sponsors in economies where the legislative framework lacks clear and coherent

definitions of, and processes for dealing with, liability, such as in relation to injuries and adverse events resulting from clinical trials. Additionally, elements such as administrative burden, gaps in resources needed for adequate regulatory review and long delays contribute to an uncertain regulatory environment that raises the costs of clinical trials and reduces incentives or ability to invest in a given market.[24]

Conversely, a clear and strong regulatory environment creates the conditions and predictability needed for the testing, production and availability of high quality products and technologies.[25] While complying with these standards may impose substantial costs on CROs, research institutions and manufacturers it also gives patients and health care providers confidence that new biomedical products are safe and effective.

### The legal environment

A strong legal system, such as a robust basis for IP protection and its enforcement in a given market, assures biomedical companies and other investors that their proprietary technologies and know-how will be protected from unauthorized use as they develop, test and launch products in that market. In particular, patents and other forms of exclusivity for biomedical products, such as regulatory data protection, provide research-based companies with an incentive to continue to make costly, lengthy and risky investments in the discovery of new biomedical products and technologies. Indeed, as Figure 2 suggests above, the development of an innovative medicine takes some 10-15 years on average.[26] Concurrently, the estimated average cost of bringing an innovative drug from development to market (including failures) is constantly rising, at around $2.6 billion by some estimates.[27] In this context, a supportive legal environment that provides necessary conditions such as robust IP protection provides firms with the protection and basis for recouping the R&D investments made, and as such an incentive to invest in the first place. Indeed, as mentioned by some estimates economies with beneficial IP protection tend to see on average 9–10 times more clinical trial activity than those lacking key aspects of IP protection.[28]

Equally important for biomedical products is rule of law and the on-the-ground enforcement of IP protections and other statutory safeguards. Key concerns for many clinical trial sponsors and research-based companies are the extent to which the production and availability of counterfeits as well as the use of parallel trade are limited and deterred.

### Healthcare resources

Clinical trials also rely on the availability of the necessary physical components, such as clinicians, hospitals and clinics, CROs, technologies, machines and instruments – as well as the medicines themselves – and the public and private funding to make it available. Indeed, high-quality human capital has been identified as essential for translational and clinical research.[29]

However, it is important to note that the availability of sufficient health care resources is an essential yet insufficient condition in increasing its clinical trials activity. A given economy's mindset and culture in relation to innovation and its ability to ensure the safety and effectiveness of medicines are equally, if not more, important to the economy's clinical trial intensity.[30]

### Market conditions

Finally, the cost-effectiveness of conducting clinical trials in a given market as well as the dynamism of the biopharmaceutical market and economy overall are typically considered as important factors of clinical research. Indeed, the last decade has witnessed an increase in global clinical trials, particularly in the BRICs.[31] However, the total number of trials conducted in these countries is still very low, and includes mostly later-stage trials which are less complex, risky and expensive.[32]

Table 2 summarizes the above key areas within the clinical research policy environment, including a sample of enabling factors within each area that are often referred to as influential in relation to clinical trial activity.

It is important to note that while these factors are all key elements in establishing an effective and competitive clinical research environment, some areas tend to have more relative importance from a statistical perspective. Specifically, there is a relative difference between the different areas discussed above when measuring the average statistical correlation of key components to clinical

trials intensity. For example, **the regulatory and IP environments and the level of available health care resources show a moderately strong to strong positive correlation to clinical trial intensity**, with the IP environment and level of resources showing the strongest correlation (from $R^2$=0.6 to $R^2$=0.8). Surprisingly, the relative cost of conducting clinical trials and the GDP growth rate, factors reflecting market conditions present in a country and typically thought of as strongly impacting the level of clinical research there, show little to no correlation to clinical trial intensity.

In sum, when it comes to enhancing economies' clinical trial activity, the clinical research policy environment matters. Where a supportive, robust and predictable clinical research policy environment exist, particularly in the areas of the legal and regulatory framework, sponsors are more likely to invest.[33] The policy trajectories taken by government officials and regulators have a real and significant impact on the investment decisions and recommendations that multinational research-based biopharmaceutical companies make. In order to enhance competitiveness, increase their clinical trial activity and benefit from the accompanying economic gains, economies – not least India – must strive to maintain a robust, high-standard and supportive clinical research policy environment. The following section will explore where India is positioned today in the realm of clinical research in terms of the level of investment and the quality of the clinical research environment.

TABLE 2 Sample of eleven enabling factors for increasing clinical trial intensity

| Category | Correlation to clinical trials intensity | Enabling factor |
|---|---|---|
| Regulatory environment | Strong/moderately strong | Compliance with global standards, i.e. GCP |
| | | Ease of recruiting and maintaining volunteers |
| | | Quality of overall clinical research regulatory environment |
| | | Timeframe for approval of clinical trials |
| IP/legal environment | Strong/moderately strong | Level of IP protection |
| | | Rule of law |
| Health care resources | Strong/moderately strong | Health spending per capita |
| | | Coverage and reimbursement of health care and medicines |
| | | Availability of skilled clinicians and infrastructure |
| Market conditions | Weak | Relative cost of conducting clinical trials |
| | | GDP growth rate |

Source: Pugatch Consilium analysis

# 3 PLACING INDIA'S BIOPHARMACEUTICAL AND CLINICAL RESEARCH ENVIRONMENT IN A GLOBAL CONTEXT

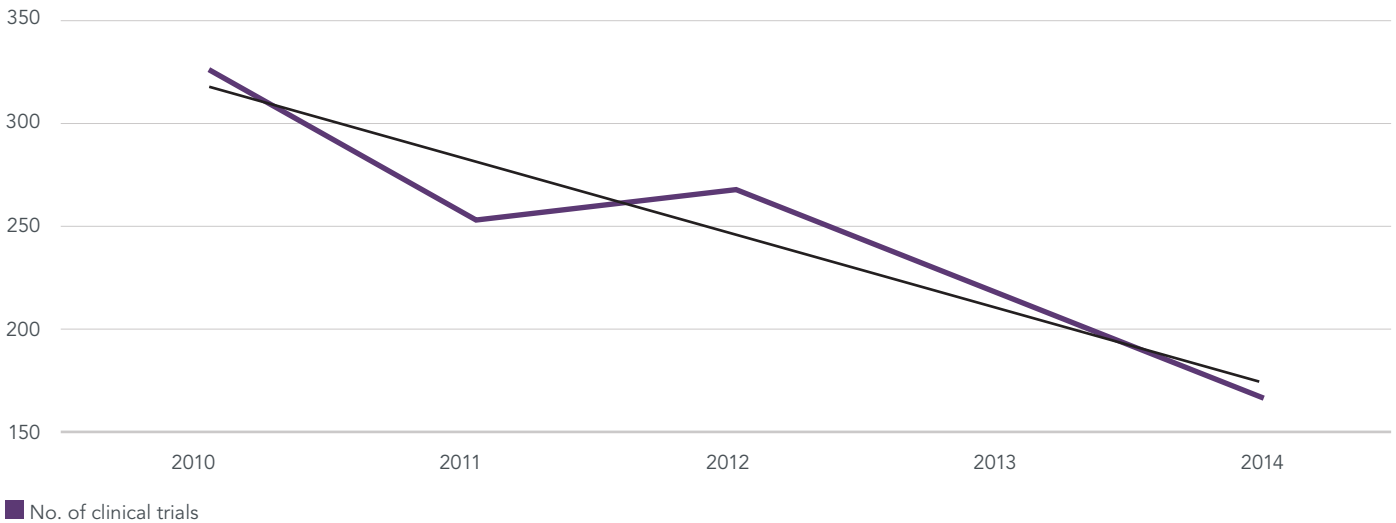
This section looks at India's current state-of-play in the field of clinical research and biomedical R&D from a broad and holistic viewpoint that takes into account all the relevant factors which constitute a given economy's clinical research policy environment. Within that context, recognizing India's position globally can illuminate both the areas that necessitate improvement and how India stands to benefit from such an improvement.

## 3.1 India's clinical trial activity in the global arena: Performing below its full potential

As mentioned, despite being a large and lost-cost market – including a population of some 1.25 billion that is in large part clinically-naïve[34] – with a strong foundation in manufacturing and contract research, India experiences a very low rate of clinical trial activity. Looking back on the past five years, India's clinical trial activity has decreased dramatically since 2013 – estimates vary depending on methodology, but at a minimum by nearly 50%, as depicted in Figure 3. This drop is likely even greater when considering high rates of trial suspension over the last few years, based on, among other elements, Supreme Court decisions and re-reviews by Ethics and Scientific Committees.[35] Indeed, by certain estimates clinical trial activity in India has fallen from over 500 clinical trials in 2011 to merely 20 in 2013.[36]

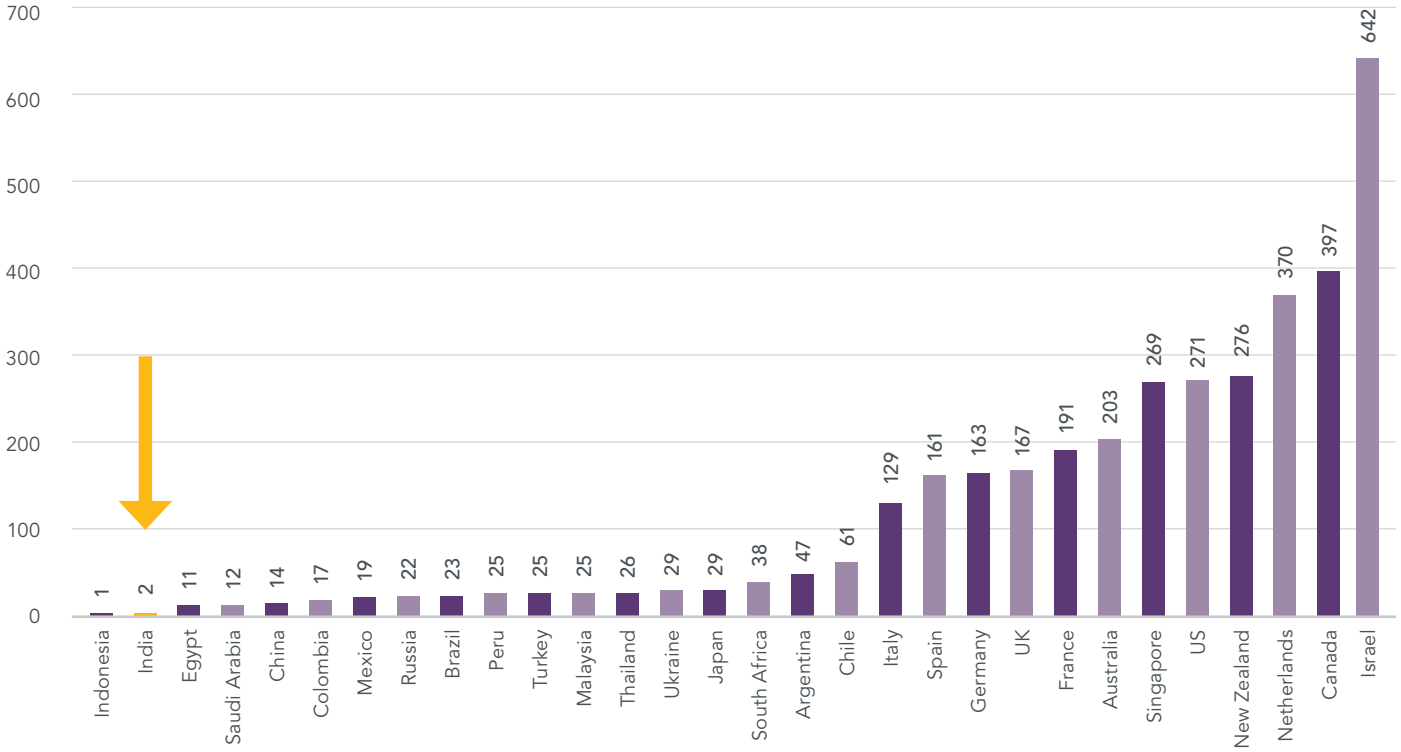
The sharp decrease in clinical trial activity in India has occurred in the context of ongoing reform activity by the Central Drug Standard Control Organization (CDCO) and the Ministry of Health and Family Welfare, including the introduction of

FIGURE 3 Clinical trial intensity in India: Annual number of new clinical trials in India, 2009-2014[38]




Source: *Clinicaltrials.gov* (2015). Based on all clinical trials first registered in a given year in India contained in the database, Clinicaltrials.gov. These included all clinical trials with a "First received" date between January 1 and December 31 of that year, and a recruitment criteria of: "Recruiting", "Active not recruiting", and "Completed". Clinical trials of all phases were included except those labeled as in "Phase 0".

FIGURE 4 Clinical trial intensity: International comparison of selected countries[40]
(based on number of clinical trials to date registered in Clinicaltrials.gov per million population)




Source: Pugatch Consilium, Clinicaltrials.gov; World Bank (2015)

more onerous clinical trial approval protocols as well as overly broad and ambiguous procedures for addressing trial-related injuries or adverse effects.[37] As will be discussed further later in this section, such regulatory changes have created a much more burdensome and unpredictable legal and regulatory framework than previously existed.

India's current clinical trial activity is also lower in comparison to many developed and developing countries. Looking, for instance, at the aggregated number of clinical trials to date registered in the global database, Clinicaltrials.gov, India hosts around only 2.11 clinical trials per million population, the lowest rate among the BRICs and near the bottom among Asian economies, as Figure 4 suggests.[39]

Moreover, the scope and complexity of clinical trials (measured by the phase of the trial and its therapeutic area) indicate the economy's capabilities and attractiveness in the global biomedical field, with early-phase trials being considered riskier and requiring more sophisticated infrastructure and skilled personnel. In this respect, as Table 3 indicates, India particularly lacks the most cutting-edge, advanced trials (such as phase II trials) as well as post-marketing trials, which are important for pharmacovigilance.

India's extremely low clinical trial activity directly affects its share in the global distribution of R&D-directed FDI. For instance, according to one industry measure, in 2013 India's share of global R&D spending by PhRMA member companies was only 0.06% – with roughly 60% of that thought to be attributed to clinical research.

TABLE 3 Clinical trials in selected countries, distributed by phase of trial, first received in 2013[41]

| Country | No. of CTs (2013) | No. of phase I trials | No. of phase II trials | No. of phase III trials | No. of phase IV trials |
|---|---|---|---|---|---|
| US | 3872 | 1223 | 1535 | 708 | 406 |
| Canada | 740 | 105 | 232 | 312 | 85 |
| UK | 694 | 187 | 202 | 238 | 67 |
| South Korea | 551 | 114 | 126 | 208 | 101 |
| China | 529 | 66 | 179 | 148 | 136 |
| Italy | 527 | 55 | 164 | 229 | 79 |
| Australia | 350 | 69 | 93 | 172 | 16 |
| Japan | 305 | 53 | 81 | 146 | 24 |
| Poland | 293 | 10 | 77 | 184 | 20 |
| Israel | 289 | 43 | 84 | 122 | 34 |
| Russia | 266 | 25 | 60 | 161 | 20 |
| Brazil | 233 | 27 | 47 | 120 | 38 |
| Turkey | 151 | 3 | 23 | 87 | 36 |
| South Africa | 144 | 14 | 35 | 85 | 10 |
| Mexico | 140 | 7 | 22 | 93 | 16 |
| Argentina | 128 | 6 | 18 | 92 | 12 |
| India | 117* | 13 | 29 | 60 | 15 |
| Thailand | 117 | 8 | 35 | 48 | 26 |

Source: Pugatch Consilium, Clinicaltrials.gov; *Registered as of 8/1/2014

TABLE 4 Global distribution of R&D spending by PhRMA-member companies in selected countries, 2013

| Geographic area | PhRMA-member companies' spending on R&D (in million US$) | % of total R&D spending |
|---|---|---|
| US | $40,396 | 78.3% |
| UK | $1,401.2 | 2.7% |
| Germany | $660.5 | 1.3% |
| Canada | $545.1 | 1.1% |
| Japan | $913.7 | 0.6% |
| China | $372.3 | 0.7% |
| France | $335.1 | 0.6% |
| Brazil | $138.1 | 0.3% |

| Geographic area | PhRMA-member companies' spending on R&D (in million US$) | % of total R&D spending |
|---|---|---|
| Mexico | $97.6 | 0.2% |
| Argentina | $97.5 | 0.2% |
| Russia | $76.9 | 0.1% |
| South Korea | $39.3 | 0.1% |
| South Africa | $39.2 | 0.1% |
| Turkey | $27.2 | 0.07% |
| India | $26.9 | 0.06% |
| TOTAL R&D | $51,613.6 | 100% |

Source: PhRMA (2015)[44]
Note: PhRMA-member company spending comprises expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies.

In sum, India punches below its weight in clinical trial activity, and equally importantly, in experiencing the economic benefits that arise from conducting clinical trials in the country. Given India's market potential, it follows then to ask why that might be? Considering the importance of clinical research policy environment to clinical trial activity, are there any gaps within India's clinical research policy environment in one or more of the areas discussed in section 2 that might be impeding India's level of clinical trial activity?

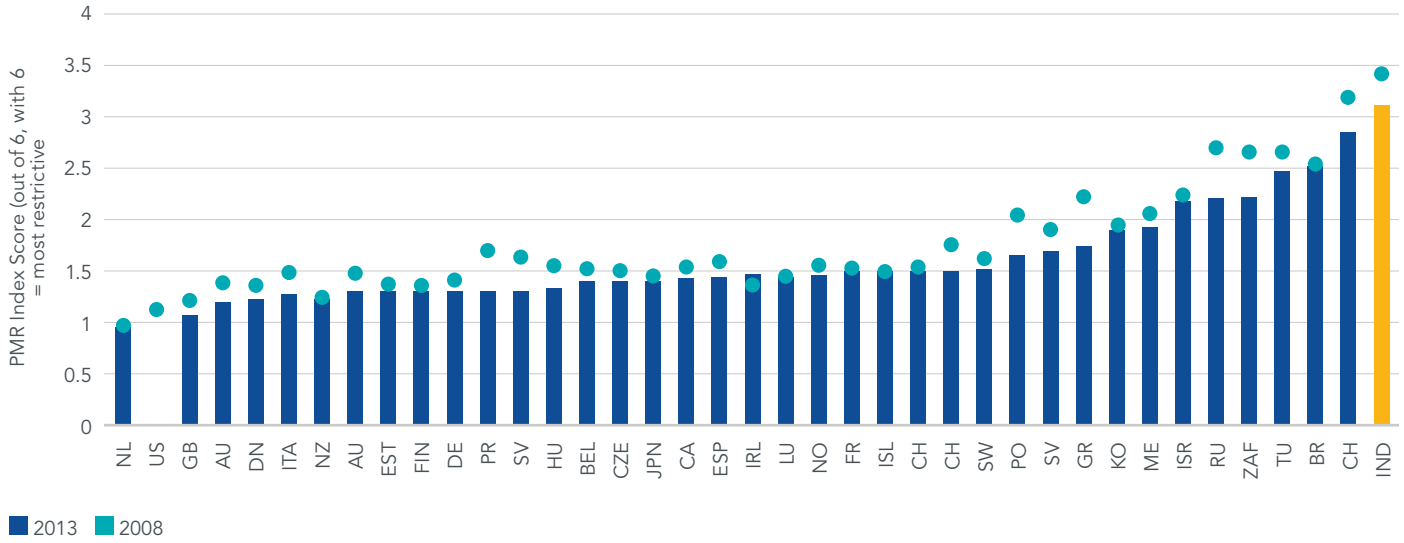
## 3.2 India's clinical research policy environment in a global perspective: Identifying gaps & challenges

Comparing India's performance in several major indicators and benchmarks related to its biopharmaceutical R&D, and specifically clinical research, environment with other leading markets suggests that there are several crucial policy areas that could be strengthened in India. This sub-section will present a brief meta-analysis of India's ranking in a number of global benchmarks of policies affecting the clinical research environment, including the quality and efficiency of the regulatory system, the strength of the legal framework, available health care resources and other market conditions – both generally and specifically for biopharmaceuticals.

### Quality and efficiency of the regulatory system

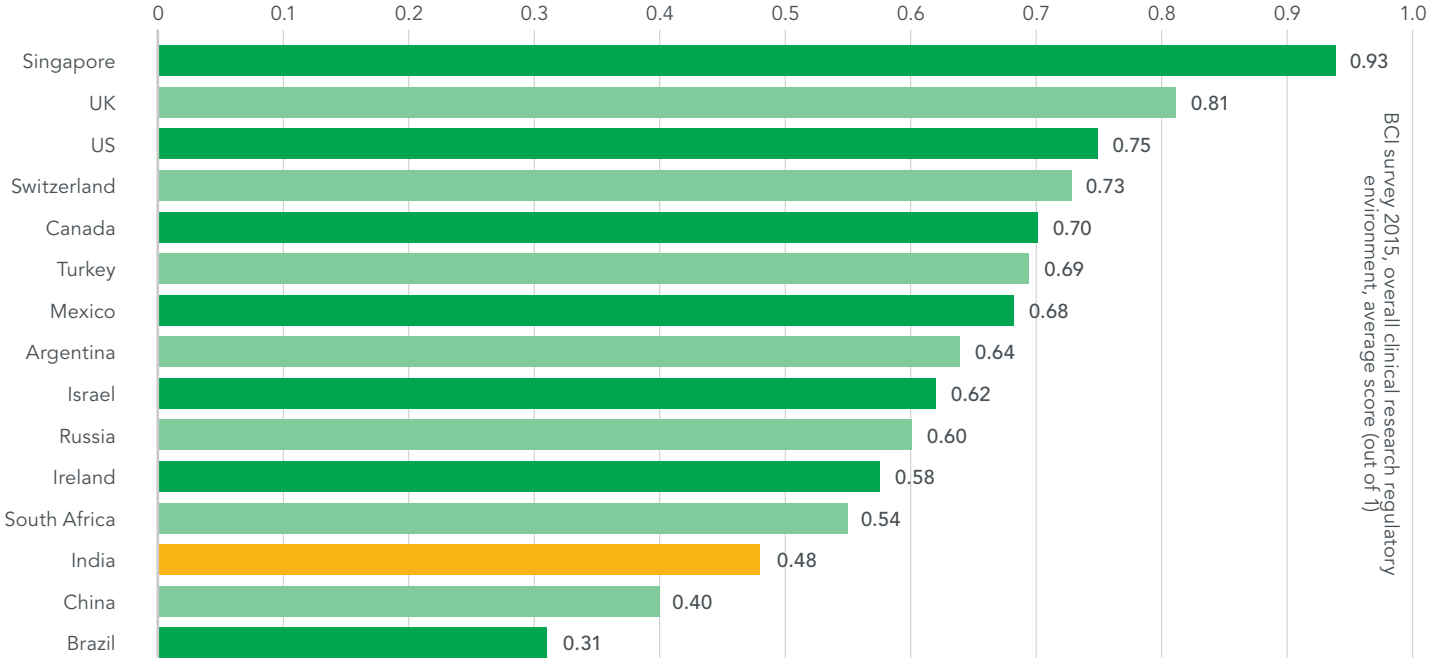
One established measure of the overall regulatory environment in a given economy is the OECD's Product Market Regulation (PMR) Index, which is a survey-based indicator of economies' product market regulation across different sectors. Though not specific to clinical research or biopharmaceutical R&D, the PMR captures many of the broader regulatory restrictions and challenges faced in regard to clinical research, such as complexity and transparency of regulatory procedures, administrative burdens and delays, inconsistencies with international standards, preferential treatment to local companies and restrictions on FDI. In the PMR Index, the higher the score, the more restrictive and challenging the market is.[45] The most recent, 2013, edition of the PMR Index reviewed OECD and non-OECD countries' regulatory environments and reforms taken since the previous edition in 2008. As Figure 5 suggests, **in this edition India is ranked at the very bottom, with its regulatory environment considered to be the most challenging among the 40 sampled countries.**[46]

FIGURE 5 India's regulatory environment in global contenxt: Product Market Regulation Index scores, 2008 v. 2013




Source: OECD (2015); U.S. data only available for 2008

FIGURE 6 Biopharmaceutical Competitiveness & Investment (BCI) Survey – 2015, Local executives' rating of the quality of overall clinical research regulatory environment in 15 economies




Source: Pugatch Consilium analysis

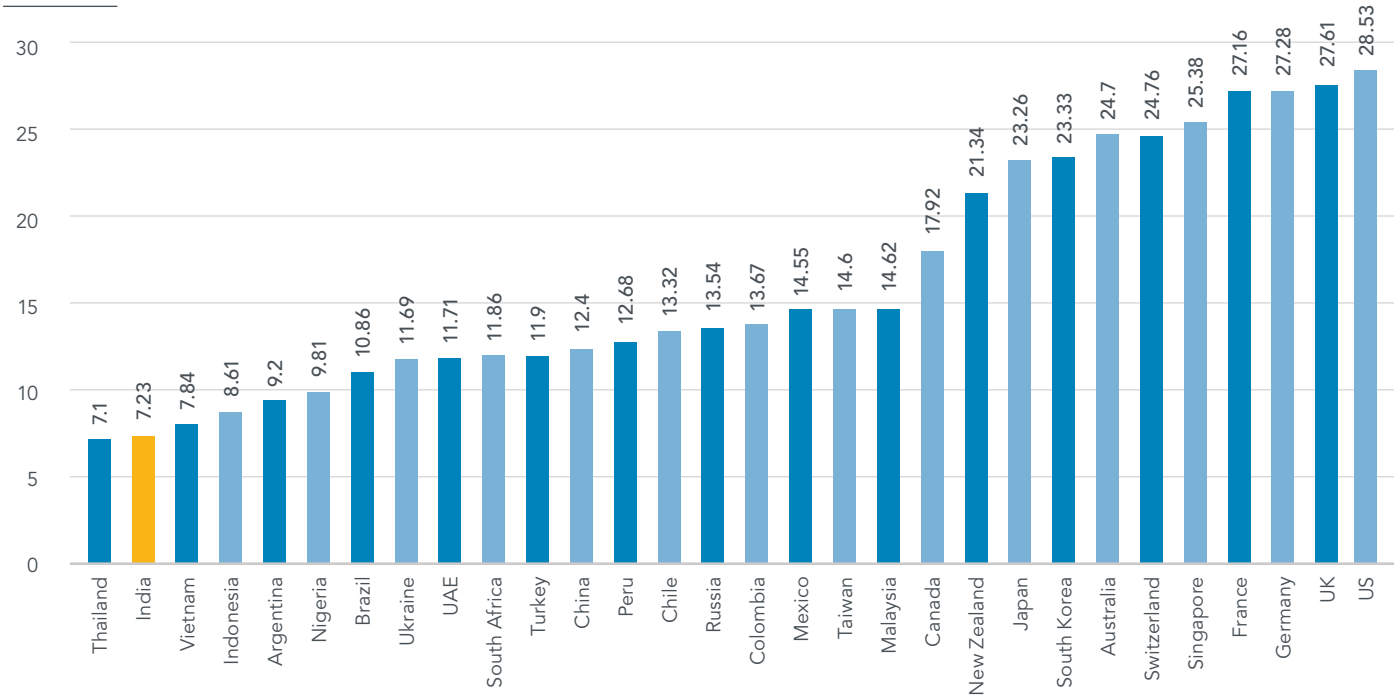
In addition, the 2015 Biopharmaceutical Competitiveness & Investment (BCI) Survey, a survey-based index of economies' biopharmaceutical competitiveness, is a measure which, among other elements, captures the quality and efficiency of the regulatory environment specifically as it pertains to clinical research.[47] The 2015 BCI results indicate that both in terms of the overall biopharmaceutical environment as well as specifically in relation to clinical research, India places in the bottom tier in a sample of 15 developed and emerging economies. Zooming in on the clinical research environment, **as seen in Figure 6 India places in the bottom group in the clinical research category, ranking 13th out of 15**. Particularly problematic areas cited by executives include a lack of transparency, predictability and quality in the regulatory framework, particularly criteria and processes for conducting and controlling clinical trials. For instance, issues raised included the need for a clear and consistently applied definition and protocol surrounding trial-related injuries, liability, approval revocation and adequate recourse mechanisms in the Drugs and Cosmetics Act in line with international best practices. The ease of recruiting volunteers and the timeframe for approval of clinical trials are also seen by local multinational executives as major areas of weakness.[48]

### The legal environment

To gauge the overall legal environment in India as it impacts biopharmaceutical R&D, the U.S. Chamber of Commerce's GIPC International IP Index is one established and up-to-date global benchmark of developed and emerging economies. A cross-sectoral measure that includes several indicators capturing the life sciences IP environment in particular, the GIPC Index provides an in-depth picture of economies' IP frameworks and level of actual enforcement on the ground.

The legal environment in India is considered quite poor with respect to other countries. **As Figure 7 shows in the 2015 editions of the GIPC Index, India ranks second to last in of a sample of 30 economies, scoring 7.23 or just under 25% of the total possible score of 30.**[49] Looking specifically at the 21 indicators in the GIPC Index that relate to the life sciences,[50] India's performance is also among the poorest, scoring around 25% of the total possible score.[51]

FIGURE 7 India's legal framework in global context: The GIPC IP Index, overall economy scores, 2015




Source: GIPC/Pugatch Consilium (2015)

Finally, the national legal environment, and particularly the rule of law, is also captured in the Global Business Rule of Law Dashboard. The meta-measure captures elements related to the rule of law particularly affecting business operations, including biopharmaceutical and life sciences companies. As Figure 8 shows, the 2015 Global Business Rule of Law Dashboard ranks India's IP environment in the lower half of the 50 countries included in the measure, scoring 49 out of a possible 100.[52]

### Healthcare resources

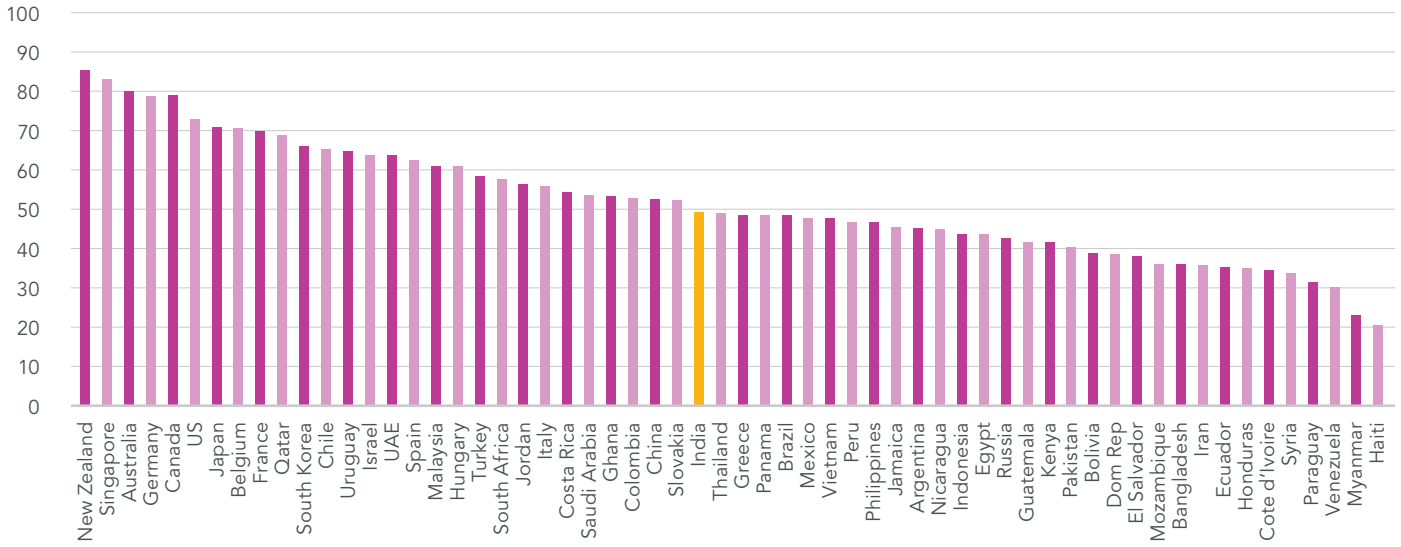
Considering the financial, physical and technological resources available for health care, medicines and clinical research, India tends to perform relatively strongly in some areas, and weak in others.

In terms of general resources available for health care, India performs quite poorly in both its level of health spending per capita as well as the level of reimbursement and coverage for health care and medicines. Based on the most recent data available from the World Bank, displayed in Figure 9, India comes in quite low in its level of health spending, with only US$215 per capita.[53] This figure represents only a fifth of the average figure in the remaining BRIC economies, and under 10% of the average among developed economies.

Looking also at the scope and extent of the coverage and reimbursement of healthcare and medicines, India's spending on pharmaceuticals lags behind many developing countries, including Asian countries and the remaining BRICs.[54] Indeed, only some 14% of new medicines launched globally in 2008-2012 were made available in India in 2013.[55]

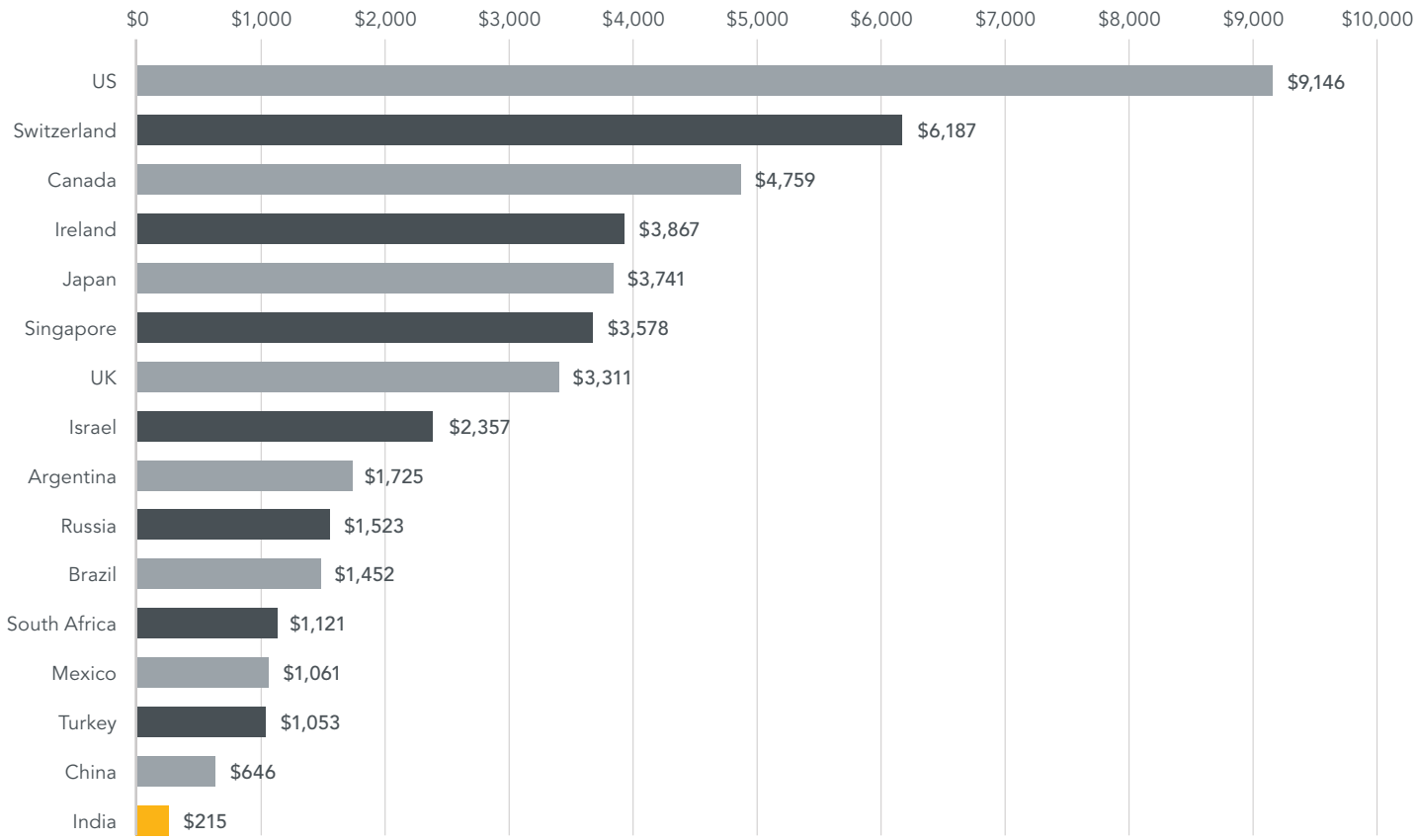
Turning to resources devoted to clinical research, India's environment is mixed. While respondents of the 2015 BCI Survey positively noted the fairly large scope and capacity of the clinical research management industry in India,[56] India's capabilities in terms of availability of skilled clinicians and infrastructure within local hospitals and clinics were viewed as limited.[57]

## FIGURE 8 2015 Global Business Rule of Law Dashboard score (0-100), 2015




Source: U.S. Chamber/Pugatch Consilium analysis

## FIGURE 9 Health spending per capita (PPP, constant 2011 International $), selected countries, 2013




Source: World Bank (2015)

### Market conditions

Finally, it is worth considering the overall market conditions affecting clinical research in India, namely the GDP growth rate and relative cost of conducting clinical trials. In this area India does quite well, with an annual GDP growth rate of 7.2%,[58] and a low relative cost of conducting clinical trials among the countries sampled in the 2015 BCI Survey.[59]

Nevertheless, as mentioned when looking at the relative importance of a wide range of factors based on a global comparison the above factors related to market conditions bear only a weak correlation to clinical trial intensity. Thus, it would be crucial to identify and strengthen other areas, including those discussed throughout this section, in order to enhance the level of clinical trial intensity in India.

Taking all the factors discussed in this section together – including the regulatory and legal environments as well as the resources available for health care and medicines – **it is clear that overall India's clinical research policy environment tends to be positioned in the lower quartile globally**.

The following Table 5 summarizes India's standing in the key global benchmarks and measures discussed in this section.

As Table 5 underscores, the areas most strongly correlated to clinical trials intensity in global terms, including the legal and regulatory environments, represent India's major areas of weakness. It stands to reason, therefore, that strengthening these fields, both generally and in particular areas of concern, would go a long way to supporting an increase in the level of clinical trial activity and the wider associated benefits across India. The remainder of the study will focus on quantifying just how much this positive impact could be depending on the degree to which improvements are made to the clinical research policy environment in India.

TABLE 5 India's clinical research policy environment: How India performs in a sample of key enabling factors

| Category | Enabling factor | India's performance and/or relative placement among sampled economies |
|---|---|---|
| Regulatory environment | Compliance with global clinical standards | 20th percentile |
| | Ease of recruiting and maintaining volunteers | 13th percentile |
| | Quality of overall clinical research regulatory environment | 20th percentile |
| | Timeframe for approval of clinical trials | 20th percentile |
| Legal environment | Level of IP protection | 7th percentile |
| | Rule of law | 52nd percentile |
| Health care resources | Health spending per capita | US$215 per capita |
| | Coverage of health care and medicines | 7th percentile |
| | Availability of skilled clinicians and infrastructure | 26th percentile |
| Market conditions | Relative cost of conducting clinical trials | 90th percentile |
| | Annual GDP growth rate | 7.2% |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# 4 METHODOLOGY

In order to quantify the direct investments and economic gains that India might expect to result from improvements to its clinical research policy environment, this study utilizes existing measures of the impact of changes to key aspects of the policy environment on foreign direct investment and associated economic gains and applies these to the case of clinical trial activity in India.

Specifically, using a statistical model the study considers what level of gains India could experience under three scenarios of policy reform on a "realistic" spectrum, that is, an improvement from the bottom quartile in a number of representative global policy measures to the median level (40-60th percentiles). For instance, achieving a performance in line with 50% of the possible score (e.g. in the BCI Survey or the GIPC or PMR indices) would require India to roughly double its score (or improve its performance by 100%).

Broadly speaking, the study is based on the following statistical model derived from established regression analyses, such as Cavazos et al. (2010):

*(Existing FDI)(% change in FDI due to policy reform) = resulting FDI + associated monetary transfers*

The remainder of this section will outline in more detail the construction and components of the model applied to the case of clinical trial activity in India.

## 4.1 Clinical trial activity and associated monetary transfers as proxies for FDI

The level of existing FDI is captured by two measures. First, clinical trial activity is measured by the number of clinical trials taking place in India in a given year as recorded by Clinicaltrials.gov.[60] In 2014 only 166 new clinical trials were registered as taking place in India.[61] **On this basis, the baseline level of clinical trial activity employed in the study's model is 166**.

The second aspect of FDI captured is the direct economic gains derived from clinical trial activity, measured by monetary flows arising from clinical research. The existing and resulting monetary flows are calculated based on spending by research-based biopharmaceutical companies on R&D per year. One challenge encountered in the study was how to measure or estimate the level of spending on R&D within the biopharmaceutical field, and specifically clinical research. Generally speaking, there is a dearth of data that accurately and adequately capture spending on clinical research in a given market, including India. Global measures tend to reflect a broader level of spending than just biopharmaceutical R&D. For instance, Battelle's annual R&D funding forecast includes data on the life sciences sectors, but not on biopharmaceutical R&D specifically. Local measures of R&D spending are also either not sector-specific or do not sufficiently capture foreign investment. On this basis, the approach taken in this study is to extrapolate total R&D spending in India by the biopharmaceutical industry specifically by a) identifying the share of industry R&D spending in India on a micro level (i.e. representative companies); and b) applying this share to the global figure on biopharmaceutical R&D spending.[62]

As such, the baseline level of R&D spending in India is derived from industry data as reported by PhRMA and IFPMA member companies. Specifically, the share of global R&D spending by PhRMA member companies (conducted by U.S.-owned companies and by the U.S. divisions of foreign-owned companies) – which, as mentioned, is approximately 0.06% based on the latest available data (from 2013). Because this figure does not include R&D performed in India by foreign divisions of foreign-owned companies, the baseline figure seeks to compensate for this as much as possible by extrapolating this share (0.06%) to the latest available global estimates on

R&D spending by the biopharmaceutical research-based industry as published by IFPMA – nearly US$140 billion in 2012.[63] Thus, by this estimate, India's share of global R&D spending can be approximated at around $86 million.

Different estimates exist as to the portion of R&D spending in the biopharmaceutical section that is typically devoted to clinical research, however, as mentioned average estimates place this figure at around 60% of annual R&D spending.[64] **Hence, the baseline figure for the existing level of spending or monetary transfers derived from clinical research is $51.4 million**. These monetary flows typically benefit or affect a wide range of stakeholders, including the key stakeholders identified in section 1, such as hospitals (including physicians), CROs, patients, payers and others.

In addition, the model takes into account that direct investments in clinical research activities are accompanied by externalities: related monetary flows which circulate through and enhance the local economy. Examples of indirect economic gains include flow of funds to vendors/suppliers, jobs in sectors supporting clinical research, etc. The economic impact of externalities is estimated by several studies at around 150-175% of the direct investments in research activities.[65] On this basis, the model measures indirect economic gains – monetary transfers associated with clinical trials –as 150% of the direct increase in monetary flows. These externalities are captured in the model as additional economic gains on top of the direct monetary flows associated with clinical trials.

## 4.2 Quantifying the increase in clinical trial activity and associated monetary transfers resulting from policy reform

The effect of policy changes on clinical trial activity and monetary transfers as types of FDI in the field of clinical research is based on existing modelling of the effect of policy change on FDI more generally. Several studies have examined the effect of improvements to national policy environments, including key areas relevant to the clinical research environment such as the regulatory system and level of IP protection, on

FIGURE 10 Constructing a model for quantifying the effect of improving India's clinical research policy environment on direct investments and economic gains, flow-chart

| | Step | Model component | |
|---|---|---|---|
| 1 | Identifying proxies for FDI and associated economic gains | FDI = | Increase in annual clinical trials activity |
| | | | Associated monetary transfers to key stakeholders (= 60% of R&D-directed investment) |
| | | Additional 150% indirect economic gains (externalities) | |
| 2 | Quantifying the increase in clinical trial activity and associated monetary transfers resulting from policy reform | Every 1% improvement leads to a 1.2% to 2.8% direct increase in clinical trials activity and monetary transfers plus additional 150% in externalities | |
| 3 | Constructing 3 scenarios for improvements | A conservative scenario (reaching on average the 40th percentile in relevant global indices) | |
| | | A moderate scenario (reaching the 50th percentile) | |
| | | An optimistic scenario (reaching the 60th percentile) | |

in-flows of FDI. For example, a recent study by the OECD found that a 1% increase in IP protection is linked to a 2.8% increase in R&D-directed FDI.[66] In addition, Nicoletti et al. (2003) tested the effect of improvements to economies' regulatory environments (as measured by the OECD's PMR Index) on FDI;[67] this study estimated that a 1% change in the regulatory environment is linked to, on average, a 1.2% increase in in-flows of investment.

Given the importance of the legal and regulatory environments to clinical research (as discussed in section 1), **the model in the present study assumes that every 1% improvement to the clinical research policy environment can lead to anywhere from a 1.2% to a 2.8% direct increase in clinical trials and monetary transfers**.

## 4.3 Constructing three scenarios applicable to India

Finally, as mentioned, on the basis of what clinical trial and economic gains would be secured if India improved its clinical research policy environment from its current position in the bottom quartile of a representative set of global indices measuring the clinical research environment to the median level, the above model is tested on three scenarios:

1. A **conservative** scenario of reaching the 40th percentile (requiring on average a 60% improvement in score in the above indices/ indicators and achieving a direct FDI impact of 72%-168%);

2. A **moderate** scenario of reaching the 50th percentile (requiring on average a 100% improvement in score and a direct FDI impact of 120%-280%); and

3. An **optimistic** scenario of reaching the 60th percentile (requiring on average a 140% improvement in score and a direct FDI impact of 168%-392%)

Figure 10 provides a stepwise flowchart of the structure of the computational model employed in this study to quantify the effect of improvement to India's clinical research policy environment on its clinical trials activity and the expected economic gains.

The following section provides the results of applying the three scenarios of improvement in India's clinical research policy environment to the above-described model.


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# 5 THE ECONOMIC GAINS OF IMPROVING INDIA'S CLINICAL RESEARCH POLICY ENVIRONMENT: KEY FINDINGS

Applying the model described in section 4 to three realistic scenarios, achieving a performance in key indicators of the clinical research policy environment of the 40th, 50th and 60th percentiles globally, respectively, suggests that India stands to benefit considerably from even a median level improvement to its clinical research policy environment.

## 5.1 The conservative scenario

Under the more conservative scenario of improving its performance from the lower quartile (or the 25th percentile) to the 40th percentile (requiring a score raise of 60%), the expected impact ranges from an increase of 72% (where 1% improvement results in an increase of 1.2%) to 168% (where 1% improvement results in an increase of 2.8%) in both clinical trial activity and associated monetary transfers, as well as an additional 150% in indirect economic gains.

As Figure 11 and Table 6 show, under a conservative scenario of reaching the 40th percentile, India could expect an addition of anywhere between 120 and 278 new clinical trials a year and up to US$344.4 million in total economic gains.

Table 7 provides an illustrative distribution of direct and indirect monetary flows accrued to key stakeholders under the conservative scenario. As is evident, even a relatively conservative improvement to the clinical research policy environment could lead to considerable benefits across key stakeholders, including discounted access to new medicines, savings to hospitals and payers and additional funding towards infrastructure and clinicians and other personnel as well as revenue supporting the growth of the local CRO industry.

FIGURE 11 Gains to clinical trial activity in a given year under the conservative scenario

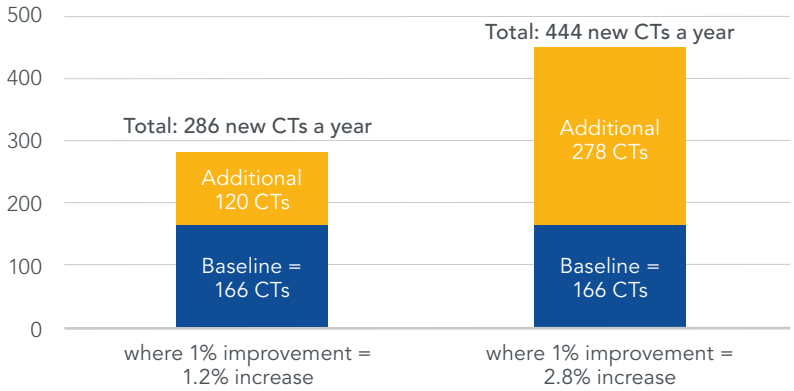



TABLE 6 Expected economic gains in a given year under the conservative scenario

| Estimated total monetary flows associated with clinical research resulting following policy reform | |
|---|---|
| Direct gain where 1% improvement = 1.2% increase | Total monetary gain (including externalities) |
| $88.4 Million | $221.05 Million |
| Direct gain where 1% improvement = 2.8% increase | Total monetary gain (including externalities) |
| $137.8 Million | $344.4 Million |

TABLE 7 Monetary and economic benefits associated with clinical trials accrued to key stakeholders under a conservative scenario of clinical research policy reform

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Hospitals & related services | $88.4 Million | $137.8 Million |
| CROs and related services | $99.5 Million | $155 Million |

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Payers | $33.2 Million | $51.6 Million |
| Other (including patients) | $33.2 Million | $51.6 Million |

## 5.2 The moderate scenario

Under the moderate scenario of improving its performance from the lower quartile (or the 25th percentile) to the median level, or the 50th percentile (requiring a score raise of 100%), the expected impact ranges from an increase of 120% (where 1% improvement results in an increase of 1.2%) to 280% (where 1% improvement results in an increase of 2.8%) in both clinical trial activity and associated monetary transfers, as well as an additional 150% in indirect economic gains.

As Figure 12 and Table 8 show, under the moderate scenario of reaching the 50th percentile, India could expect an addition of anywhere between 199 and 465 new clinical trials a year and up to US$488.4 million total economic gains.

Under the moderate scenario, as Table 9 shows, a rather small increase in improvement in the policy environment above that of the conservative scenario leads to a significant increase in gains to key stakeholders, with wider benefits for public health, cost containment and industrial development.

FIGURE 12 Gains to clinical trial activity in a given year under the moderate scenario

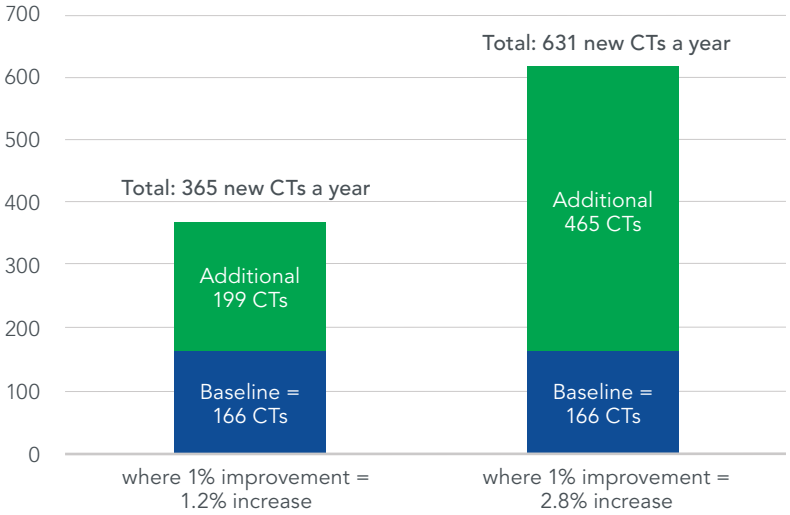



TABLE 8 Expected economic gains in a given year under the moderate scenario

| Estimated total monetary flows associated with clinical research resulting following policy reform | |
|---|---|
| Direct gain where 1% improvement = 1.2% increase | Total monetary gain (including externalities) |
| $113.1 Million | $282.7 Million |
| Direct gain where 1% improvement = 2.8% increase | Total monetary gain (including externalities) |
| $195.4 Million | $488.4 Million |

TABLE 9 Monetary and economic benefits associated with clinical trials accrued to key stakeholders under a moderate scenario of clinical research policy reform

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Hospitals & related services | $113.1 Million | $195.4 Million |
| CROs and related services | $127.2 Million | $219.8 Million |

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Payers | $42.4 Million | $73.3 Million |
| Other (including patients) | $42.4 Million | $73.3 Million |

## 5.3 The optimistic scenario

Under the more optimistic scenario of improving its performance from the lower quartile (or the 25th percentile) to the 60th percentile (requiring a score raise of 140%), the expected ranges from an increase of 168% (where 1% improvement results in an increase of 1.2%) to 392% (where 1% improvement results in an increase of 2.8%) in both clinical trial activity and associated monetary transfers, as well as an additional 150% in indirect economic gains.

As Figure 13 and Table 10 show, under the optimistic scenario of reaching the 60th percentile, India could expect an addition of anywhere between 278 and 651 new clinical trials a year and up to US$632.3 million in total economic gains.

Again, as in the other scenarios, Table 11 suggests that rather small steps in improvements to India's clinical research policy environment could lead to significant increases to direct monetary gains to key stakeholders, and wider micro and macro-level contributions. In this case, if India's policy environment reached the 60th percentile in global terms, key stakeholders stand to benefit at least 60% more in terms of monetary and economic gains than under the conservative scenario. To put these gains in perspective, the overall gains estimated in this scenario of around $1.24 billion represent a significant portion of India's total annual spending on medicines – around 5%.[68]

FIGURE 13 Gains to clinical trials activity in a given year under the optimistic scenario

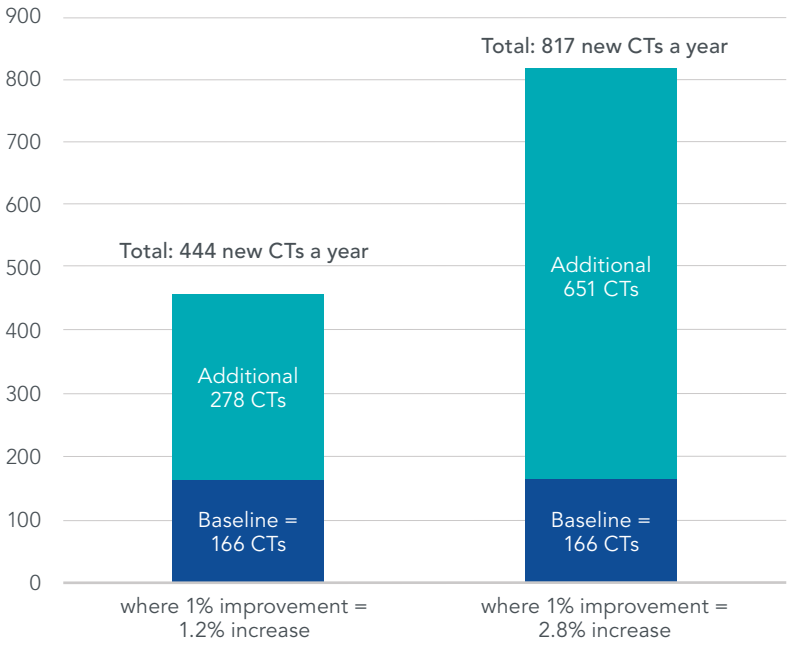



TABLE 10 Expected economic gains in a given year under the optimistic scenario

| Estimated total monetary flows associated with clinical research resulting following policy reform | |
|---|---|
| Direct gain where 1% improvement = 1.2% increase | Total monetary gain (including externalities) |
| $137.8 Million | $344.4 Million |
| Direct gain where 1% improvement = 2.8% increase | Total monetary gain (including externalities) |
| $252.9 Million | $632.3 Million |

TABLE 11 Monetary and economic benefits associated with clinical trials accrued to key stakeholders under an optimistic scenario of clinical research policy reform

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Hospitals & related services | $137.8 Million | $252.9 Million |
| CROs and related services | $155 Million | $284.5 Million |

| Stakeholder | Bottom of range | Top of range |
|---|---|---|
| Payers | $51.7 Million | $94.8 Million |
| Other (including patients) | $51.7 Million | $94.8 Million |

# 6 A PROPOSED BLUEPRINT FOR SECURING GREATER ECONOMIC GAINS IN INDIA FROM THE FIELD OF CLINICAL RESEARCH

As discussed throughout this report, clinical trials have crucial public health, social and economic benefits that align with many strategic policy objectives of governments today – from enabling local access to needed cutting edge treatments, and building domestic biopharmaceutical sectors to supporting containment of health care and pharmaceutical costs and driving wider economic gains.

Coming from a relatively low starting point in its current level of clinical trial activity – one of the lowest rates of annual clinical trials globally – India is a country that stands to benefit significantly from greater clinical trial activity.

This study has analyzed India's clinical research policy environment in relation to international best practices, and in so doing identified which policy improvements support greater clinical trial activity in the country and quantified the resulting wider, positive economic effects. For this purpose, a new model has been created that:

a) quantifies the level of clinical trials currently taking place in India as well as its clinical research policy environment compared to other leading markets;

b) statistically measures which aspects of the policy environment matter most for clinical trial intensity; and finally,

c) considers the effects of policy reform on investment in clinical research based on previous studies and international experience, providing scenario analysis of the impact of key policy improvements in India on its number of clinical trials, FDI and additional externalities.

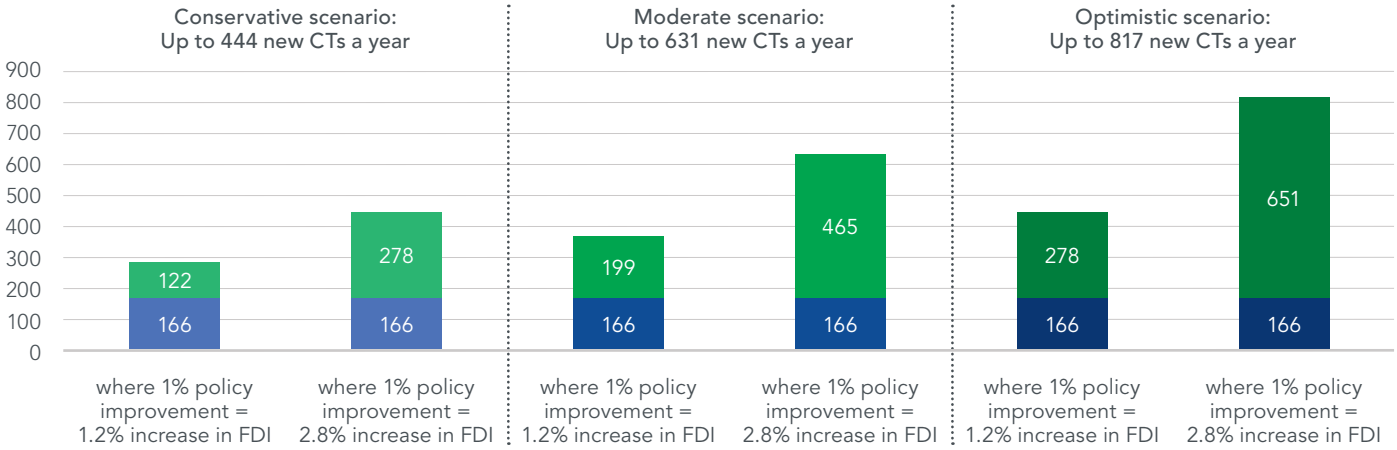
## Key findings

The study firstly shows that key factors in today's low clinical trial intensity in India relative to other leading markets include existing policy challenges in the country related to clinical research, particularly in relation to the regulatory system, legal framework and resources enabling the capacity for conducting and controlling clinical research.

Indeed, as it stands now the regulatory system in India vis-à-vis clinical research faces major challenges, not least important gaps in predictability and transparency in the criteria and processes governing clinical research outlined in the Drugs and Cosmetics Act, and continuing to exist in amendments to this legislation available earlier in 2015. These include clinical trial approval protocols as well as procedures for addressing trial-related injuries or adverse effects.

Moreover, a high level of uncertainty and antagonism exists towards certain aspects of the legal framework. India's patentability requirements remain outside established international best practices; in the past 3-4 years India has discussed the use of compulsory licensing, and in one instance issued a compulsory license, on bases outside its obligation under the TRIPS Agreement; and there is a lack of specific biopharmaceutical IP rights such s regulatory data protection. In addition, research-based companies in India can experience drawn-out litigation and difficulties securing meaningful and timely remedies for infringement.

FIGURE 14 Estimated gains to clinical trial activity in a given year, based on three scenarios within a median level of policy reform




Source: Pugatch Consilium; Note: the 3 scenarios roughly equate to the median level of international best practices identified in key relevant global benchmarks (e.g. OECD, 2013; GIPC, 2015); the methodology used to calculate the baseline figure of 166 clinical trials in India in 2014 is outlined in detail in the methodology section

In addition, the Indian drug regulatory agency, at both the central and state levels, lacks adequate resources for needed capacity building, funding and infrastructure in order to ensure a high quality and efficient clinical research system in India.

As a result of these and other policy issues affecting clinical research India tends to place in the **bottom quartile** in global benchmarks related to the clinical research policy environment, such as the 2015 GIPC International Intellectual Property Index, the OECD's 2013 Product Market Regulation (PMR) Index and the 2015 Biopharmaceutical Competitiveness & Investment (BCI) Survey.

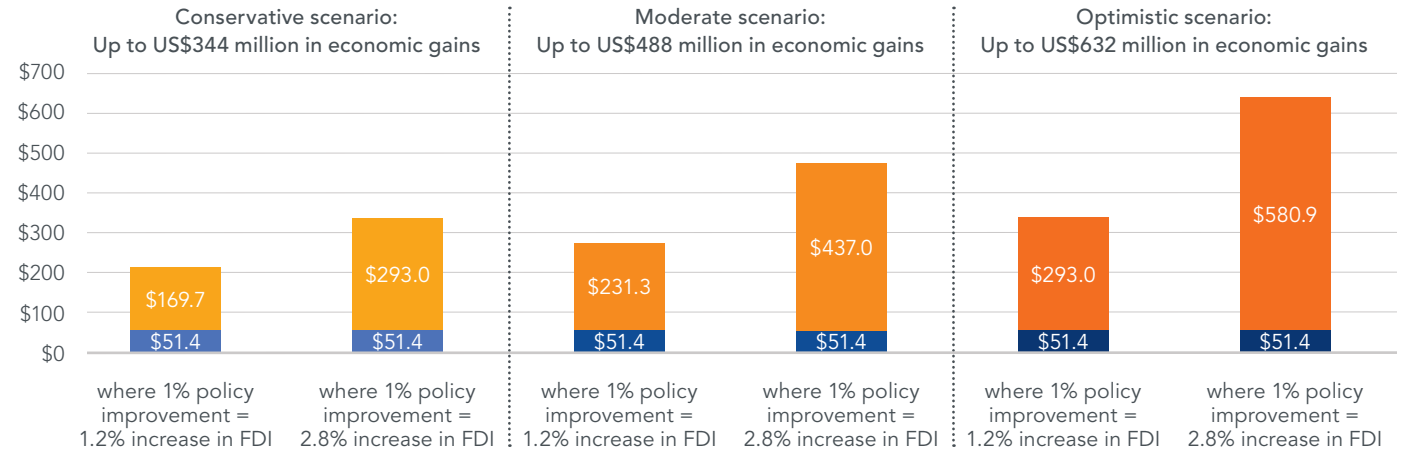
Yet at the same time, numerous empirical studies suggest that improvements to the policy environment and addressing outstanding concerns could have a significant impact on attracting and securing greater investment and associated economic gains. This study has shown that even small improvements to the Indian clinical research policy environment, for instance in the areas outlined above, could result in considerable gains across the Indian public health system and economy.

The following two figures summarize the key investment and economic gains estimated to arise from policy improvements that would allow India to reach roughly the median percentile (40th to 60th) on representative global benchmarks such as those mentioned above. The range of expected gains are estimated based on the modeling in key studies such as from the OECD, Nicoletti et al. (2003) and Cavazos et al. (2010), which find that a 1% policy change leads to a 1.2% and 2.8% increase in FDI, respectively.

In other words an improvement in India's clinical research policy environment that roughly equals the median level of international best practices as quantified in this study could **increase India's number of new clinical trials per year to above 800 and add close to 1 billion dollars in direct monetary transfers and indirect economic gains**. This may be regarded as a conservative estimate; it is possible India could experience even higher levels of investment and economic gains.

In order for India to secure the full level of investment and monetary and economic gains identified in this study and modeling, Table 12 outlines the most urgent policy elements needing to be addressed in India within the area of clinical research.

FIGURE 15 Estimated economic gains in a given year associated with clinical trial activity, based on three scenarios within a median level of policy reform




Baseline level of economic gains from clinical trials in a given year (based on latest available data)

Estimated minimum level of economic gains from clinical trials following policy reform

Source: Pugatch Consilium; Note: the 3 scenarios roughly equate to the median level of international best practices identified in key relevant global benchmarks (e.g. OECD, 2013; GIPC, 2015)

TABLE 12 Current improvements required in India's clinical research policy environment

| Policy area | Policy improvements needed |
|---|---|
| Regulatory framework | • In the Drugs and Cosmetics (Amendment) Bill 2015 and amendments to the Drugs and Cosmetics Rules, 1945:<br>– Include a clear definition and protocol surrounding trial-related injuries and liability in line with international best practices<br>– Clarify procedures for clinical trial approval revocation and suspension of the Ethics Committee, and introduce adequate recourse mechanisms<br>– Provide for a transparent and predictable site inspection process<br>• Ensure the above is also consistently applied in practice |
| Legal framework | • Strengthen the patent system by removing barriers to entry and enhancing predictability<br>• Harmonize the Indian patent system with international best practices<br>• Introduce regulatory data protection |
| Health care resources | • Increase targeted funding and resources to the Indian drug regulatory agency at both the central and state levels aimed at capacity building and greater efficiency |

Source: Pugatch Consilium, PhRMA, 2015


OH
$H_3C$
$H_3CO$
$OCH_3$
$OCH_3$
N
$H_3CO$
$H_3CO$
OH
10.215
10.365
10.596

# NOTES

[1] For instance, see Pugatch Consilium (2015), *Measuring the Global Biomedical Pulse: The Biopharmaceutical Competitiveness & Investment (BCI) Survey 2015*, p. 11.

[2] Ibid.

[3] Pugatch Consilium (2014), *Scaling Up Global Clinical Trial Activity: Key Trends and Policy Lessons*, p. 35. Note: the five-year period refers to 2009-2013.

[4] Pugatch Consilium (2014)

[5] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "History and Future", www.ich.org/cache/compo/276-254-1.html

[6] US Food and Drug Administration (FDA), "The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective", www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm

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[9] Ibid., p.1.

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[17] US FDA, "Basic Questions and Answers about Clinical Trials", www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm121345.htm; PwC (2010), *Clinical Trials in Poland: Key Challenges*, p. 48; EDCTP (2010), p. 2

[18] See for instance: Sertkaya et al. (2014), *Examination of Clinical Trial Costs and Barriers for Drug Development*, Commissioned by US Dept for Health and Human Services, p.3-6; Battelle (2015), *Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies*, Commissioned by PhRMA, p.6

[19] Note: Given that different stakeholders may benefit from the same monetary transfers associated with clinical research, overlap exists between their shares of total expenditure. In addition, the portion of clinical trial expenditure accrued to different stakeholders here accounts for different in type/phase of trials conducted by using the average share of total spend across all types of trials.

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[21] Pugatch Consilium (2014)

[22] Berndt, et al. (2007), "The Globalization of Clinical Trials for New Medicines: Where are the Trials Going and Why?", iHEA 6th World Congress; Bramley-Harker, et al. (2007), "Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry", Prepared by NERA Economic Consulting for UK Trade and Investment; A.T. Kearney (2006), "Make Your Move: Taking Clinical Trials to the Best Location", A.T. Kearney Executive Agenda; Pugatch Consilium (2015)

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[28] Pugatch Consilium. (2014), p. 35; Note: the five-year period refers to 2009-2013.

[29] Bairu, M. & Chin, R. (2012). *Global Clinical Trials Playbook: Capacity and Capability Building*, Academic Press, p. 111.

[30] Pugatch Consilium. (2014), p. 29.

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[32] Pugatch Consilium (2014); A.T. Kearney (2006)

[33] See, for instance, U.S. Chamber Global Intellectual Property Center (GIPC), *UP: Unlimited Potential*, GIPC International IP Index, Third Edition, February 2015, p. 4.

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[35] See for example: Chowdhury, A. (2013). "New Rules Slow Down Pharmaceutical Trials in India", *The Wall Street Journal*, 7/11/2013, www.wsj.com/articles/SB10001424127887324251504578579542215585484; IHS, "Indian Clinical Trials Decline 93% in 2013", 1/28/2014, www.ihs.com/country-industry-forecasting.html?ID=1065985147

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[37] For a detailed description of the reforms, see for instance: Sanghavi, D. (2013), "Regulatory Reforms in India", *Journal of Therapeutic Innovation & Regulatory Sciences*, Vol. 47, Issue 1, pp. 16-18

[38] This figure was created using latest available data (as of July 2015) from *Clinicaltrials.gov*, capturing only clinical trials registered on the database in a given year and labeled as either "recruiting", "active but not recruiting", and "completed" in India. This method aims to account for trials that were recorded in the database as cancelled or suspended (though this is likely still a conservative estimate of trial cancellations and suspensions).

[39] Pugatch Consilium (2014); *Clinicaltrials.gov*, a registry maintained and regularly updated by the US National Institutes of Health, contains data on clinical trials taking place in 187 countries, including India. It is important to note that a key challenge faced in producing this report concerned how to measure the number of clinical trials taking place in a given country – using which source and on what basis. First, in terms of source, although there is no central database of all clinical trials being conducted worldwide, there are a handful of websites that provide information on clinical trials on an international scale, with Clinicaltrials.gov being one of the most robust. Second, clinical trials are difficult to measure because there are no established parameters for the unit of measure or the time frame. Bearing this in mind, with regard to unit of measurement, in this report we have opted to take as broad an approach as possible, with the idea that in future analyses it will possible to narrow the parameters to control for different types of clinical trials. Specifically, this report counts as clinical trials interventional studies registered in *Clinicaltrials.gov* that test the effect of medical products (such as drugs, devices and procedures) on human volunteers.

[40] Based on number of registered clinical trials within the *Clinicaltrials.gov* database as of 2015.

[41] Based on number of registered trials within the *Clinicaltrials.gov* database, listed with a start date of 2013.

[42] PhRMA (2014), *The Biopharmaceutical Industry Profile: 2014*, p. 72.

[43] IMS White Paper (2012), *Restoring innovation as global pharma's center of growth: How to optimize clinical trial performance and save $1 billion annually*, IMS Health, p.1

[44] PhRMA (2014)

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[46] Ibid.

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[48] Ibid.

[49] GIPC (2015), p. 22.

[50] Of the 30 indicators in the GIPC Index, the life science-related indicators consist of those falling under the Patent, Trademark, and Trade Secrets and Market Access categories of the GIPC Index, as well as those indicators in the Enforcement and Membership in International Treaties categories that are relevant to the life sciences (specifically: 1-2, 4-7, 14-21, 23-26, and 28-30).

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[52] Pugatch Consilium/U.S. Chamber, *A Natural Pairing: The Rule of Law and Business: Expanding the Global Business Rule of Law Dashboard*, 2015

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[54] IMS Institute for Healthcare Informatics (2014), p.6.

[55] Ibid., p. 24.

[56] Pugatch Consilium (2015)

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[58] IMF (2015), *World Economic Outlook: Uneven Growth – Short- and Long-Term Factors*, p.54, April 2015

[59] For instance, among the 15 economies covered in the 2015 BCI Survey, India scored the lowest in the area of costs of conducting clinical trials. Source: Pugatch Consilium (2015), pp. 48-49.

[60] See: www.clinicaltrials.gov.

[61] Based on all clinical trials registered in 2014 in India contained in the database, *Clinicaltrials.gov*. Analysis included applying filters which included only clinical trials with a "first received" date within 2014, and a recruitment criteria of: Recruiting, Active not recruiting, and Completed. Registries with "phase 0" were excluded, but all other registries of phases (including registries with no entries in the phase rubric) were included. Analysis was performed on MS Excel.

[62] Battelle (2013), *2014 Global R&D Funding Forecast*, pp.22-23

[63] IFPMA (2014), *The Pharmaceutical Industry and Global Health: Facts and Figures 2014*, p. 13

[64] IMS White Paper (2012), *Restoring innovation as global pharma's center of growth: How to optimize clinical trial performance and save $1 billion annually*, IMS Health, p.1.

[65] See for example: Battelle (2015), *Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies*, Commissioned by PhRMA, p.9; Sertkaya et al. (2014), *Examination of Clinical Trial Costs and Barriers for Drug Development*, Commissioned by US Dept for Health and Human Services, p.3-6.

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