

The Case for Globalization: Ethical and Business Considerations in Clinical Research

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Executive Summary

As clinical trials have become increasingly globalized over the past ten to fifteen years, the possibility of conducting studies that offer adequate subject protection and yield reliable results in emerging countries has understandably attracted considerable attention. In this analysis, we examine the facts regarding the current state of clinical research and the role that biopharmaceutical companies and their clinical research organization (CRO) partners play in ensuring that the dual goals of trial safety and quality are met.

Although concerns have been raised about the globalization of biomedical research, the reality is that emerging countries play a vital role in the advancement of medical science. Clinical trials in these countries, particularly those with industry sponsorship, are conducted at the high standards necessary to obtain regulatory approval in major markets. In addition, the investments made by trial sponsors, which are frequently implemented by CROs, are a major contributor to improving the health systems and economies of the developing world.

Among the key findings of this report:

- Increased demand for clinical trial subjects combined with lower participation rates in developed countries has the potential to dramatically slow the progress of medical science. Indeed, VOI Consulting estimates that it would require approximately 5.8 years to fully enroll all currently open Phase III cancer trials if only U.S. locations were used as compared to 1.9 years using both U.S. and global trial sites.
- While trials in emerging countries have received an enormous amount of attention in recent years, the vast majority of clinical research continues to be conducted in countries with well-established infrastructures. A few statistics point out just how big a role the U.S., Western Europe and other developed regions continue to play:
 - Member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) spent approximately 96% of clinical phase dollars in developed countries during 2007.

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- In its September 2008 report on CROs, Frost & Sullivan estimates that North America has a 49% share of global R&D spending while Western Europe had a 37% share. The share for Asia Pacific, a region that includes established markets such as Japan and Australia as well as emerging centers such like India and China, is approximately 13.5% and the rest of the world has only 0.5%.
- Seventy-six percent of all Phase I studies take place in just three countries, the U.S., Canada and the Netherlands.
- Analysis of data from ClinicalTrials.gov shows that 51.8% of all newly registered industry-sponsored trials in 2008 had at least some U.S. activity; the exact same share as in 2006. This compares with India's 2.7% participation rate, China's 1.8%, Russia's 3.3% and Mexico's 2.4%.
- Trials in emerging countries are subject to the same standards that prevail in the developed world. This is especially true of industry-sponsored trials as these are ultimately aimed at gaining regulatory approval for new products. To engage in unethical or poor quality research is to run the risk that the product will be rejected, leaving the sponsor no way to recoup their R&D investments. The power of the market to correct improper practices is shown by a 2009 incident in which a U.S.-based commercial Institutional Review Board was forced to close due to client losses just one week after receiving an FDA warning letter.
- Regulatory and cultural norms regarding clinical research in emerging countries are often more, rather than less, strict than in developed regions. Examples of this include the difficulty of conducting early phase studies in India and placebo-based studies in Latin America. Patients in these countries may also seek greater input from friends and family before deciding to enroll in a trial.
- Clinical research plays an important role in improving the health systems and economies of emerging countries. In Poland, for example, 30% of hospital cancer therapy is funded by clinical trial sponsors.
- The term "emerging market" disguises a wide range of experience levels. After 15 years of experience with clinical trials, capabilities of the larger Central European countries are

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considered to be very nearly on a par with those in Western Europe. Other countries, such as South Korea and Taiwan, have advanced medical infrastructures and should be considered “emerging” only in the sense that their trial activity is growing rapidly.

- Working with CROs offers a number of advantages for sponsors involved in emerging country trials. In addition to the benefits of reduced costs and faster time to market, CROs provide standardization of operating procedures (SOPs) and, at the same time, are more likely to have a deeper understanding of local language, culture and norms, qualities which lead to better relations with investigators and improved trial execution.
- The presence of CROs benefits host countries as well. They provide advanced equipment and trained personnel, offer high paying jobs in areas where employment opportunities are scarce and have been instrumental in harmonizing research norms in emerging countries with developed world standards.

Although legitimate concerns have been raised in the past about clinical trials in emerging countries, the ability to conduct high quality studies in these locations has been enormously improved over the previous ten to fifteen years. Rather than placing further barriers to drug development, efforts should be focused on enhancing the progress that has already been made while continuing to train and monitor researchers throughout the world to ensure their compliance with the highest standards. As this report demonstrates, much of this is already being done as part of the normal business practices of biopharmaceutical companies and CROs, all of whom have a major stake in a strong and improving clinical research environment.

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Introduction

Since 1948 when results of the first randomized clinical study were published,¹ clinical trials have become the established cornerstone of medical research. Clinical trials are now “an integral part” of the “rigorous approval process” employed by the U.S. Food and Drug Administration to show that drugs and medical devices have been “determined to be safe and effective for their respective indications.”²

Given that clinical trials are a necessary precondition for gaining regulatory approval for a medical product, it is not surprising that approximately 75% of clinical studies are funded by companies that seek to market drugs and devices.³ Indeed, pharmaceutical and biotech companies are the greatest contributor to research on a global scale,⁴ spending approximately \$130 billion on R&D in 2008.⁵ Of this amount, 60 to 70% was spent on clinical stage activities.^{6,7} Although it has been said that “the profit motive of commercial research can conflict with participant protection and the scientific validity of clinical trials,”⁸ researchers in non-profit fields are often similarly motivated by monetary research grants, opportunities for career advancement and prominence, and even individual pecuniary gains that come from finding medical advances. While the risk of conflicts must be managed by both for-profit and non-profit institutions, monetary rewards associated with successful research often serve to fuel the achievement of life saving medical cures and this holds true whether the research takes place in a commercial or academic environment. To place excessive restrictions on clinical research would clearly have damaging repercussions for global health, in both a physical and economic sense. As the U.S. Department of Health and Human Services’ Office of the Inspector General has stated, “the critical challenge is to ensure essential human-subject protections without unnecessarily slowing the pace of research and discovery.”⁹

Like many scientific and business activities, clinical research has experienced a significant degree of globalization in recent years. This trend towards international clinical studies has raised a number of

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issues, of which the major concerns are the ethical treatment of participants and the quality of the resulting research.

More precisely, these concerns are not about international trials as such. Few would argue that Canada, Australia, Japan and the countries of Western Europe are not on a par with the United States in terms of ensuring that patients are recruited in an ethical manner, that trials are conducted in safe, well-regulated environments and that studies produce reliable results. Concerns are focused, instead, on increased clinical trial activity in emerging locations such as India, China, and the countries of Latin America, Central and Eastern Europe (CEE) and Africa.

This analysis examines the need for global clinical research and looks at the facts regarding the nature of clinical trials in emerging countries. The focus is on the role of the pharmaceutical industry and their clinical research organization (CRO) partners. Research on human beings is one of the most ethically serious activities that human beings engage in and, as such, rightly deserves to be subject to clear rules and rigorous enforcement. As will be shown, trials conducted with industry sponsorship meet the highest ethical and quality standards, regardless of where they are performed; research capabilities found in developing countries are much stronger than is commonly perceived; and the involvement of emerging countries in clinical research advances medical science while also contributing to the improvement of health systems and economies.

The Context of Global Clinical Trials

Approximately half of all pivotal studies submitted to the FDA contain at least some foreign data.¹⁰ Between 2004 and 2007, the number of FDA-regulated investigators increased by 15.9% in Central and Eastern Europe (CEE), by 12.1% in Latin America and by 10.2% in the Asia-Pacific region. Meanwhile, the number of North American and Western European investigators declined by 5.2% and 6.1%, respectively.¹¹

Lower cost is the usual reason cited for conducting clinical trials in emerging markets and this is an important factor. The cost per patient in India and China has been estimated at one-third of that in the United States.¹² Although per patient costs are lower, when logistical and other factors are

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considered, the fully-loaded cost of conducting studies in developing countries often approaches levels that would be found in more established areas.¹³ In truth, the largest benefit of globalized trials comes from faster time to market – reducing development time by half results in nearly two-thirds reduction in overall development cost and provides a longer post-approval patent term in which to recoup the investment.¹⁴ Faster trials also mean that patients are able to access safe and effective medicines more quickly.

While business considerations are important for trial sponsors, of greater relevance for society is the fact that if trials were restricted to established research markets where only some 15% of the world's population lives,¹⁵ it would simply not be possible to successfully recruit sufficient numbers of patients to fill the growing demands of clinical research. It has been estimated, for example, that the number of patients required to fill all spots in industry-sponsored trials increased from 2.8 million in 1999 to 19.8 million in 2005.¹⁶

A number of factors are driving this rapid growth. Consider that as of February 2009, there were approximately 2,900 new drug compounds in clinical trials or undergoing FDA review, a 52.6% increase over 1999 levels.¹⁷ Further, the average number of days to complete a trial grew by 70% from 1999 to 2005 while enrollment rates declined by 21% and retention rates fell by 30%.¹⁸

As a result of low participation rates in developed countries, trials are unable to recruit sufficient numbers of patients on schedule. Only seven percent of trials in the U.S. begin on time and 70% are delayed for more than a month.¹⁹ In the United Kingdom, 30% of investigative sites in industry-sponsored trials fail to recruit a single patient and 70% of sites fail to meet recruitment targets.²⁰

Along with a growing level of research activity, longer trials and lower participation rates, the number of patients per trial is also increasing across all phases of clinical research. A recent survey by the French industry association, *Les entreprises du médicament* (LEEM), found a 40% jump in the number of enrolled patients in studies conducted by major pharmaceutical companies between 2006 and 2008 alone.²¹ As shown in Table 1, the same survey found that trial sites in more established countries recruited an average of 7.2 patients in 2008 while sites in emerging areas were 63% more

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productive with an average of 11.8 patients. Notably, site productivity in the United States, which was already low in comparison to other locations, actually declined in the two year period.

Table 1 - Number of Patients Enrolled per Active Trial Site: Established versus Emerging Markets²²

Established Markets	Patients per active site 2008	Change (in patients) since 2006	Emerging Markets	Patients per active site 2008	Change (in patients) since 2006
France	7.6	+ 1.3	Eastern Europe	13.0	+ 2.6
Germany	8.3	+ 1.5	Latin America	11.4	+ 2.3
United Kingdom	8.1	+ 2.5	Asia	11.1	+ 0.1
Canada	6.5	+ 0.3			
United States	5.7	- 0.4			
Average Above Countries	7.2	+ 1.0	Average Above Regions	11.8	+ 1.7

The above figures indicate that the involvement of emerging countries is absolutely necessary if medical research is to continue advancing at the rapid pace to which we have become accustomed. As a single illustration, it has been reported that only three to five percent of U.S. cancer patients participate in clinical trials.^{23,24} Using the higher figure of five percent, VOI Consulting estimates that it would require approximately 5.8 years to fully enroll all currently open Phase III cancer trials if only U.S. locations were used. This compares to 1.9 years using both U.S. and global trial sites. This 3.8 year reduction in development time translates to improvements in pharmaceutical industry performance and, of greater importance, faster access to life-saving therapies for patients. Further, these estimates are based only on currently open trials; if new trials were added without clearing the backlog, the time needed to bring new drugs to market would continue to grow. (See Appendix A for methodology and calculations.)

Although emerging markets have experienced rapid growth in recent years, it is important to understand their role in the overall context of drug research. In fact, the U.S., Western Europe and other developed countries continue to host the vast majority of clinical trials. After all, the converse of the above-mentioned statistic that half of all pivotal studies submitted to the FDA contain some foreign data is that approximately half of these studies *include no foreign data whatsoever*. Given the

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degree of attention that global trials have received in recent years, this is a somewhat more surprising finding.

VOI Consulting analysis of data from ClinicalTrials.gov shows that 51.8% of all newly registered industry-sponsored trials in 2008 had at least some U.S. activity; the exact same share as in 2006. This compares with India's 2.7% participation rate, China's 1.8%, Russia's 3.3% and Mexico's 2.4%.²⁵ This method is not perfect as ClinicalTrials.gov may tend to over-represent U.S.-based research. Nonetheless, all reliable sources support the finding that clinical research is still very much dominated by countries with established research histories. For example:

- In 2007, member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA), a list that includes U.S. as well as many major foreign firms, spent only 3% of all R&D dollars in emerging countries. Preclinical activity accounts for 27.3% of total spending and it is likely that virtually all preclinical work was done in regions with established research capabilities. If we remove preclinical expenditures, the total amount of R&D spent in developing countries rises to 4.1%.²⁶
- In its September 2008 report on CROs, Frost & Sullivan estimates that North America has a 49% share of global R&D spending while Western Europe had a 37% share. The share for Asia Pacific, a region that includes established markets such as Japan and Australia as well as emerging centers like India and China, is approximately 13.5% and the rest of the world has only 0.5%.²⁷
- Eighty-three percent of active investigative sites are in the developed countries of North America, Western Europe and Oceania.²⁸
- The United States had 36,281 sites authorized to conduct clinical trials in 2007. This represented nearly half (48.9%) of all globally authorized sites. In contrast, twelve leading emerging research countries had a combined total of approximately 7,400 authorized sites, or 20% of the U.S. number.²⁹
- India is believed to have accounted for just 0.1% of R&D budgets from U.S. pharmaceutical companies in 2006.³⁰
- Approximately 70% of FDA-regulated investigators are in the U.S. or Western Europe.³¹

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- Seventy-six percent of all Phase I studies take place in just three countries, the U.S., Canada and the Netherlands, all of which possess highly advanced research capabilities. Although emerging countries may eventually play a larger role in Phase I bioequivalence studies for established drugs, it is expected that “the more novel, sophisticated, complex [Phase I] studies [will] predominantly play out in North America and Western Europe.”³²

Although only a small portion of research currently takes place in emerging countries, concerns have been raised about the nature of the studies that are done in these regions. A 1996 Nigeria-based trial of the antibiotic, Trovan (trovafloxacin), is frequently cited as an example of research that would not have been allowed to proceed in more developed markets. The exact facts of the case are in dispute and, as of mid-2009, it appears that Pfizer, the trial sponsor, and the plaintiffs are close to reaching an out-of-court settlement.³³ According to some reports, however, the researchers failed to obtain informed consent and the trial resulted in the deaths of 11 children.³⁴

Obviously, it is extremely troubling when research subjects experience harm of any kind, and even more so when these subjects are children. It is nonetheless important to note that this trial took place more than a decade ago when international research was in a far less mature state than at present. Today, emerging countries exhibit stronger ethical and regulatory oversight, greater institutional capacity and higher levels of professionalism. As we will see, the driving force behind these improvements has been the experience gained in trials run by pharmaceutical companies and their CRO partners.

The Clinical Research System

Clinical research on humans is subject to certain ethical and regulatory norms. Although these may be interpreted or implemented somewhat differently from one country to another, they stand as general principles that apply to studies regardless of where they are performed. To understand the implications of conducting trials in developing countries, it is important to first understand these global norms.

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The Nuremberg Code, which arose out of the post-World War Two “Doctor’s Trial”, serves as the ethical foundation of human research. The Code consists of ten principles, of which the most important states that “the voluntary consent of the human subject is absolutely essential.” The Code also states that the subject must be in a position to “exercise free power of choice” based on accurate information and free from “any element” of coercion. In addition, “the experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means”; “the degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved”; and “during the course of the experiment the human subject should be at liberty to bring the experiment to an end.”³⁵ The principle of informed consent has been called the most important contribution of the Code and has been widely adopted by the research community.³⁶

The other major guiding document is the Declaration of Helsinki, first published by the World Medical Association in 1964. One of its biggest contributions was to introduce the ethics committee (EC).³⁷ The Declaration states, “the [trial] protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.”³⁸ The role of the EC is to ensure that the benefits of a study outweigh its risks, that patients are properly informed about their rights and the risks involved in participation and that they are not subject to undue pressure to enroll (e.g. via excessive payments). In addition to providing initial review, the EC is charged with reviewing the trial on an ongoing basis³⁹ (a step that takes place in parallel with regular monitoring by the sponsor or CRO).

Ethics committees go by various names around the world including Institutional Review Boards (or IRBs in the U.S.), Research Ethics Boards (REBs, Canada), Research Ethics Committees (RECs, many Western European countries), Helsinki Committees (Israel), Bioethics Committees (Poland) and Committees for Ethical Protection (CEPs, Brazil). Although more established research markets often offer centralized ethical review for multi-site trials, these committees are usually housed within the

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institution that is considering whether to host the study. In addition to medical professionals, EC membership generally includes consumers as well as legal and ethical experts.

Clinical trials must also receive some form of approval from a legally authorized regulatory authority. The Guideline for Good Clinical Practice (GCP) from the International Conference on Harmonisation (ICH) provides the principles for regulatory oversight. Originally adopted by the U.S., Japan and the European Union in 1996, ICH-GCP has since been written into the laws of many emerging research countries and is followed uniformly by CROs throughout the world.

Ethical Considerations

None of the benefits of greater access to clinical trial populations are worthwhile if the patients involved are subjected to undue risk or if the studies themselves fail to provide reliable results. This raises a number of questions about international research such as:

- At a general level, what social justice concerns are raised by human research in developing countries and how are these different from concerns in developed countries?
- Are existing patient safeguards adequate to protect research participants and ensure quality results?
- Are the rules protecting patients effectively enforced?

Social Justice Issues

One common complaint about globalized research is that the pharmaceutical industry uses poor countries to test drugs that will benefit rich countries. Specifically, it is has been asserted that trials tend to focus on chronic conditions associated with aging rather than acute infectious diseases that plague the developing world.⁴⁰

While tropical diseases are not generally a main focus of pharmaceutical companies, neither are they completely ignored. A 2008 study by CenterWatch found “19 drugs in various stages of development against tropical diseases related to bacterial, viral and parasitic infections.” These included vaccines and prophylactic agents as well as agents to combat existing infections.⁴¹ Admittedly, this represents

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a small percentage of the previously mentioned 2,900 total drugs in development but there are enormous variations in the number of people that an individual agent can help. Penicillin, for example, has likely saved millions of lives since it was first used in the early 1940s.⁴² Further, deaths from tropical diseases are in many cases more a function of infrastructure than drug therapy. This is shown by an April 2009 study from the WHO which reported that deaths from malaria declined 47% in Zambia between 2006 and 2008 following the distribution of 3.6 million insecticide-treated bed nets.⁴³

In any case, to criticize the for-profit pharmaceutical industry for conducting research that will result in profitable products ignores the fact that, by definition, patients enrolled in a clinical trial suffer from the condition being studied. While cancer might not be a major cause of death *within a country*, individual patients are faced with a single cause of death and, if they have cancer, then that is the *single cause of death* they are most likely facing.

We argue that conducting trials in the developing world should be considered unethical only if patients there are treated differently than those in developed countries. For example, if trials in poor countries have a higher rate of randomization to placebo, then this does present a serious ethical problem. It appears that such differential treatment has indeed happened in isolated cases in the past. As shown later in this analysis, however, rising experience levels have strengthened the institutions charged with oversight in developing countries and raised awareness among developed world regulators about the potential for abuse and the need to scrutinize the quality of clinical research.

It is also worth repeating that “first-in-human” trials – i.e. Phase I research on investigational agents – are almost exclusively conducted in countries with advanced capabilities. (Although emerging markets may report Phase I activity, these tend to be bioequivalence studies used to show that a generic drug possesses the same qualities as a well-established branded product.) First-in-human research is generally conducted on healthy volunteers and therefore offers the subject no therapeutic benefit. While certainly not risk-free, the Phase II and later trials that are much more

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likely to be conducted in developing countries represent a potential for patients to benefit directly from the investigational drug.

Although problems with trials sponsored by multinational companies are likely to receive more press attention, ethical and quality violations often occur in trials initiated by local investigators. In 2002 and 2003, for example, Indian doctors initiated several unauthorized trials of cancer, contraceptive and fertility agents, none of which involved participation by Western sponsors.⁴⁴ Exposure to developed world research procedures and strict adherence to industry-standard GCP will more likely serve to reduce rather than exacerbate these problems. This is demonstrated by 2008 study on the quality of clinical trials in China. Although the authors found problems with the way in which trialists reported their findings (for example, inadequate discussion of informed consent procedures), it was also apparent that researchers in Western-medicine trials, at least some of which were presumably sponsored by pharmaceutical companies or CROs, were in greater compliance with standard practices than were researchers involved in trials of Traditional Chinese Medicines.⁴⁵

Clinical research also provides benefits well beyond the direct effects of the therapeutic intervention. Patients get access to a standard of care that might otherwise be unavailable, investigators are exposed to advanced medical techniques and the larger society benefits from improved health infrastructure and economic development.⁴⁶ Phase II and Phase III trials, in particular, tend to result in new investment and job growth.⁴⁷ For example, Western pharmaceutical companies spent only \$30 million on trials in India in 2004.⁴⁸ By 2006, this had reached \$140 million⁴⁹ and by 2010 total investment is expected to reach \$1.5 billion.⁵⁰ In a country where total 2005 spending on health was approximately \$42 billion,⁵¹ this represents a significant infusion of capital.

In countries that are particularly strapped for health care funds, clinical trials also provide a major source of subsidized medical treatment. For example, a 2006 study by Pricewaterhouse Coopers reported that approximately 30% of hospital cancer therapy in Poland is funded by clinical trial sponsors.⁵² It is difficult to understand how withdrawing these subsidies would be an improvement in either medical or ethical terms.

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Patient Safeguards

The two most common concerns surrounding patient protection in trials conducted in developing countries are whether proper informed consent can be obtained and whether payment offered for participation exerts undue pressure on poor patients. Incidentally, essentially the same concerns have been expressed by the Department of Health and Human Services' Office of the Inspector General regarding trial recruitment in the United States.⁵³

Informed Consent

Table 2 shows literacy rates for sample countries in the emerging and established categories. Literacy might be considered a reasonable proxy measurement for the ability to grant informed consent based on an understanding of the implications of trial enrollment. Unsurprisingly, rates in emerging countries are lower than in the developed world. For the most part, however, the differences are less than might be expected. Countries in Central and Eastern Europe exhibit literacy rates comparable to, or in some cases higher than, advanced economies while China, Thailand, Argentina and Mexico are all above 90%. The average literacy for these countries (93.5%) is well above the world average of (82%). One notable exception is India, where only 61% of the population is literate. Even here the implications for informed consent are better than that statistic would indicate when one considers that clinical research is conducted primarily in urban areas and, per the 2001 Indian Census, literacy in urban areas is substantially higher (80.3%) than in rural areas (59.4%).⁵⁴

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Table 2 - Literacy Rates in Sample Emerging and Established Trial Locations⁵⁵

Emerging Trial Locations	Literacy Rate	Established Trial Locations	Literacy Rate
Argentina	97.2%	Australia	99.0%
Brazil	88.6%	Canada	99.0%
China	90.9%	Denmark	99.0%
Czech Republic	99.0%	France	99.0%
Hungary	99.5%	Germany	99.0%
India	61.0%	Italy	98.8%
Mexico	91.0%	Japan	99.0%
Poland	99.8%	Netherlands	99.0%
Romania	97.3%	Norway	100.0%
Russia	99.4%	Spain	97.9%
Slovakia	99.6%	Sweden	99.0%
Singapore	92.5%	Switzerland	99.0%
South Africa	86.4%	United Kingdom	99.0%
South Korea	97.9%	United States	99.0%
Taiwan	96.1%		
Thailand	92.6%		
Ukraine	99.4%		
Unweighted Average Literacy Rate	93.4%	Unweighted Average Literacy Rate	99.0%

World Average 82.0%

Basic literacy is, of course, no guarantee that a patient can understand the implications of trial enrollment, but poor understanding of the nature of clinical research is hardly confined to the developing world. In Germany, for example, parents of children asked to participate in a trial of an investigational attention deficit and hyperactivity drug had difficulties understanding the nature of the placebo comparative arm and did not properly understand that the primary objective of the study was research rather than the best individualized medical care.⁵⁶ Indeed, “the tendency among patients to have an optimistic bias and therapeutic misconceptions about trials” is well-documented, regardless of where the research takes place.⁵⁷

One factor that may help protect developing world patients from participating in a trial against their interest is the greater involvement of family and friends in the decision-making process. A recent study in India, for example, found that 92% of patients involved other people before deciding to enroll in a trial while only 62% of U.S. patients did so.⁵⁸

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Undue Influences

Another commonly raised ethical concern about research in poor countries is that the monetary compensation provided for participation can be sufficient in and of itself to constitute undue influence.⁵⁹ It should be noted that research norms dictate that any payments associated with the trial be examined as part of the ethical review process and that subjects in Phase II and later trials (i.e. those who actually have the condition being studied) are usually paid very low amounts. Standard practice is to reimburse for meals, transportation and similar out-of-pocket expenses related to participation in the trial. Healthy volunteers in Phase I trials may be paid substantially more but, as discussed elsewhere, these studies take place almost exclusively in the developed world.

It is true that even a small amount of money may be a considerable enticement in very poor countries. Nonetheless, the argument over whether this constitutes undue influence ignores the fact that patients in the developed world are also subject to pressures that are extrinsic to the trial itself. In the United States, for example, 45.7 million people or 15.3% of the population did not have health insurance in 2007.⁶⁰ As a result, they may be “especially willing to participate in research insofar as they consider it a way to get health care or treatments that are otherwise unavailable to them.”⁶¹

Further, in many countries with universal health care systems, patients must endure extensive waiting periods prior to receiving appropriate care. A few examples:

- From the time they receive a general practitioner’s referral for inpatient treatment, patients in the U.K. National Health System must wait an average of approximately two months (8.6 weeks) before they are admitted to the hospital.⁶²
- Canadian patients face even longer waiting times: in 2008, the averages were 8.5 weeks between GP referral and a specialist visit, then an additional 8.7 weeks from the specialist visit to receiving care, a combined total of 17.3 weeks. Candidates for neurosurgery and orthopedic surgery had to wait a total of 31.7 and 36.7 weeks, respectively.⁶³

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- Swedish guidelines call for 80% of lung cancer patients to receive a treatment plan within 28 days of diagnosis but none of the country's health regions actually meet this goal. In the capital, Stockholm, only 34% of patients receive a treatment plan within the target period.⁶⁴

It is reasonable to assume that the faster access to care that might be available to patients via trial participation serves as a motivating factor in these situations.

With the above considerations in mind, it is worth noting that pharmaceutical companies earn the vast majority of their revenues in developed countries.⁶⁵ Even if we ignore all ethical research norms, it would clearly be extremely poor business strategy to invest in research that would ultimately be rejected by regulatory agencies in these major markets. What sort of policies, then, do regulators and other government authorities have regarding ethical conduct of trials conducted outside their borders?

- According to FDA regulations that went into effect on October 27, 2008, all foreign studies conducted in association with a drug or medical device approval must follow GCP guidelines. The new regulations require independent ethical committee (IEC) review and oversight, documentation of IEC, investigator and site qualifications, the ability for onsite FDA inspection and sponsor maintenance of records for at least two years following the FDA's decision on the application. Sponsors must also explain how they obtained informed consent and this must include a description of incentives provided to participants. Monitoring and GCP training procedures must also be described. These regulations apply to all foreign clinical studies regardless of whether they are new, ongoing or completed.⁶⁶
- The European Union will not recognize the results of trials anywhere in the world if these violate the prevailing ethical standards of the developed world.⁶⁷ According to the "Additional Protocol" of the Council of Europe's Convention on Human Rights and Biomedicine (CHRB), studies carried out by "sponsors or researchers within the jurisdiction of a Party to this Protocol [i.e. in E.U. countries]" that takes place in a country outside the jurisdiction of the Protocol must comply with the terms of the Protocol if they differ from those in the other country. The Additional

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Protocol was specifically drafted with globalized clinical research in mind and ensures that clinical research complies with high standards, regardless of where it is conducted.⁶⁸

- A January 2009 ruling by the U.S. Court of Appeals for the Second Circuit found that obtaining informed consent from research subjects has become a “universal norm” accepted by the civilized world. In practical terms, this represents a very meaningful restraint against unethical behavior as it opens up the possibility for plaintiffs to sue in U.S. courts under the Alien Tort Statute.⁶⁹

In addition to the safeguards put in place by developed world agencies, the domestic regulatory and legal systems of emerging research centers provide another layer of patient protection. Indeed, developing countries often have regulations or norms that are more stringent than in established regions. For example, until a few years ago, trials in India were subject to a “phase lag.” This meant that to initiate a Phase II trial in India, it was necessary that the agent be under study in a Phase III trial somewhere else in the world. Under regulations that were revised in 2005, this requirement was dropped. However, it is still not possible to conduct a Phase I trial in India for new drug substances discovered elsewhere unless Phase I data from other countries is available.⁷⁰ Argentina and Brazil are examples of locations where sponsors will have a very difficult time obtaining ethical or regulatory approval for trials with placebo-based comparative arms unless no other proven therapy exists.⁷¹

Interestingly, in many developed countries, regulatory agencies provide tacit rather than explicit consent. In other words, sponsors may proceed with a trial unless they are informed otherwise within a certain (relatively short) period of time. In Germany, for example, trial authorization for most investigational agents may be assumed if the regulatory agency does not communicate objections to the sponsor within 30 regulatory days after receipt of the appropriate documents.⁷² Australia has an even more expeditious approach: 95% of all studies are approved via the Clinical Trial Notification scheme whereby the regulatory agency does not review any information relating to the protocol, instead placing the onus of responsibility for approval on one of the country’s Human Research Ethics Committees.⁷³

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By contrast, laws governing research in the major emerging research countries universally require explicit approval by the regulatory agency; China, India, Poland, Russia, Argentina, Brazil and South Africa are among the locations that use the explicit approval approach. In addition, regulatory procedures in emerging countries are more likely to require protocols to undergo sequential rather than parallel reviews by the EC and regulatory authorities.⁷⁴

The goal in pointing out these differences is not to disparage the quality, ethical or otherwise, of trial approval methods used in countries with established research capabilities. By definition, regulators and researchers in these places have more experience with trial evaluation and monitoring. As emerging regions gain exposure to world-class standards and techniques, it is likely that their regulatory systems will move in the direction of expedited approval. In the meantime, however, the requirement for explicit approval (and in most cases, sequential review) provides another layer of oversight in less developed countries.

Research practices in developed countries can also be inconsistent or incomplete. Indeed, it has been said that there is a “huge diversity in national regulations” regarding clinical research.⁷⁵ For example, France has more lenient rules than the United States concerning which studies require approval from an ethical committee.⁷⁶ A U.K. study found that 16% of authors of papers on interventional trials did not specify whether they had obtained ethical approval for their studies.⁷⁷ Another author writing on the ethical review process in the U.K. cites “a continual process of radical change” and “inherent variability in moral judgment.”⁷⁸

Quality Safeguards

In addition to ethical treatment of study participants, the other major concern is how the involvement of emerging countries affects research results. The issues at stake include whether the data was accurately assessed, captured and reported; whether the trial environment was in compliance with developed world standards; and whether the trial was conducted and reported without bias.

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Table 3 below shows the results of FDA clinical investigator inspections for the period 2000 to 2008. Note that “No Action Indicated” means that no objectionable conditions or practices were found during the inspection; “Voluntary Action Indicated” means that problems were found but they were not sufficient to justify regulatory action and the choice of whether to correct the problems was left to the investigator; “Official Action Indicated” means that problems sufficient to warrant regulatory actions were found. Although it is true that only a relatively small number of inspections have been conducted in emerging trial countries (or any other country outside the United States), the inspections that have been done indicate that the quality of research is in line with developed world norms. Indeed, inspections in the U.S. have yielded a higher percentage of “Official Action Indicated” findings than in any other country.

Table 3 - Results of FDA Clinical Investigator Inspections 2000-08⁷⁹

	No Action Required	Voluntary Action Indicated	Official Action Indicated	Total
Africa	41%	59%	0%	29
Asia/Pacific, other	63%	38%	0%	16
Australia/New Zealand	50%	50%	0%	4
Canada	33%	67%	0%	94
Central, Eastern Europe	42%	57%	1%	183
China	6%	94%	0%	17
India	40%	60%	0%	10
Japan	100%	0%	0%	1
Korea	0%	100%	0%	2
Latin America	31%	67%	3%	117
Middle East	18%	73%	9%	11
US	25%	65%	10%	4,014
Western Europe	25%	74%	1%	314
Total	1,248	3,157	407	4,812

Although FDA inspections were slow to adapt to the rising level of global trial activity, significant strides have been made in recent years. For example, the number of international GCP inspections doubled from 50 in 2000 to 100 in 2007 when foreign inspections represented 10% of total bioresearch monitoring activity.⁸⁰ The FDA has or soon will open offices in China and India as well as

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in Europe, Latin America and the Middle East. This began in November 2008 with new locations in Beijing, Shanghai and Guangzhou, China. In early 2009, offices were opened in New Delhi and Mumbai, India.⁸¹ The first Latin American office was started in Costa Rica in January 2009; this will be followed with a direct FDA presence in Mexico and South America later in the year.⁸² Initially, the primary task of these new offices will be to monitor manufacturing quality. However, inspections of research sites will also be conducted and are likely to increase in number over time.⁸³

In another effort to improve research oversight, the FDA has recently changed from a policy of conducting inspections as part of the application review process or in response to complaints to a more proactive approach of reviewing ongoing trials. This allows for problem identification and corrective measures while the study is still underway. The FDA is also doing more follow-up work to determine whether corrective measures were taken in trials found to be in violation.⁸⁴

As previously mentioned, European regulatory authorities require that trials conform to the same ethical and quality standards regardless of whether they are conducted within the E.U. or elsewhere. Since 2005, all marketing authorization applications must contain information “regarding the location of conduct and ethical standards applied in respect of clinical trials conducted in [non-E.U.] countries.” In 2006, the European Medicines Agency (EMA) established a system of routine GCP inspections with particular focus on developing countries and studies in which vulnerable populations, including children, are enrolled. As part of its 2009 action plan, the EMA announced that it will conduct these inspections “at earlier stages before and during the conduct of the clinical trials.”⁸⁵

The Role of Market Forces in Clinical Research

Given that the debate over the quality of studies conducted in developing countries is somewhat intertwined with the debate over the role of for-profit companies in clinical research, it is worth noting that no form of research is completely immune from the potential for bias. Pressures faced in purely academic research include the need to obtain grant funding and to advance careers through publication of successful studies. Unlike non-commercial research, industry-sponsored trials are also subject to additional scrutiny as part of the product approval process. In the U.S., the FDA “may

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consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting and analysis of the studies to minimize bias.”⁸⁶

Further, in the U.S. a higher number of deaths in trials with healthy volunteers have involved studies approved by academic rather than commercial IRBs.⁸⁷ In a 2008 article, Ezekiel J. Emanuel, chairman of clinical bioethics at the National Institutes of Health, reported that the FDA has issued “hundreds of warning letters to academic IRBs” but this has happened only once in the case of for-profit IRBs.⁸⁸ In April 2009, the FDA sent another warning letter to a commercial IRB. The outcome of this case, however, confirms the existence of strong market forces dictating that industry-sponsored researchers conform to very high standards. It is difficult to imagine an academic center closing its doors after receiving an FDA warning letter related to its ethical review process but this is exactly what happened with Coast IRB. According to the Wall Street Journal, “an April 14 warning letter from the Food and Drug Administration describing the company's violations led several high-profile customers to pull their business. As a result, ‘Coast IRB's owners decided, through counsel, to cease future company operations.’” This announcement occurred just one week after receipt of the warning letter.⁸⁹

Improving Environments

The blanket term “emerging market” actually disguises a wide range of experience levels. Poland, the Czech Republic, Hungary and Romania are among the CEE countries with expanding research capabilities that are members of the European Union and, as such, are subject to the E.U. Clinical Trials Directive (CTD). This has led to “considerable” improvement in GCP-compliance in the CEE region since 2004.⁹⁰ As a result of the CTD and the experience gained by researchers during more than a decade of working on trials, many experts now consider that, while these countries continue to offer relatively rapid patient recruitment, they are actually mature markets with clinical research capabilities very close to those of Western Europe.⁹¹

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Looking further east to Russia, the first trials sponsored by Western pharmaceutical companies took place as far back as 1993. Since then, the country has adopted international GCP and has participated in well over 1,000 international multicenter trials. Approximately 90% of trial monitors have medical doctorate degrees.⁹² In 2008, there were 946 institutions authorized to host clinical research and the Russian regulatory authority, RZN, approved 615 new trials during the year. Fifty-nine percent of these were multinational, multi-center trials. In the fourth quarter of 2008 alone, the FDA approved 12 new drugs, expanded indications, manufacturing or formulation changes relying in part on studies that involved Russian participation. The EMEA made 10 approval decisions that involved Russian data during the same period.⁹³

Considering the relatively advanced state of clinical research in CEE countries, it is worth noting that although the combined population of the entire region is less than half that of either China or India, the number of trials initiated in the CEE during 2007 was more than double that of the entire Asia-Pacific region.⁹⁴

Similarly, while countries like South Korea and Taiwan are included in the emerging category, this is more a reflection of rapid growth than of a lack of scientific or medical expertise. Indeed, both countries have invested considerable amounts to increase their attractiveness as locations for advanced research. In 2006, for example, the government of South Korea announced a \$14.3 billion program to build the country's biomedical research capabilities.⁹⁵ Taiwan has named biomedicine one of six priority industries to improve the country's global competitive position, thereby building on a clinical research history which goes back to at least 1993.⁹⁶

In the same way that wide variations exist between "emerging" countries, there are also significant differences between the capabilities of various institutions within a single country. As the Rand Institute has noted, it is possible that "a world-class [scientific or technological] capability exists in what would otherwise be called a developing country."⁹⁷ As an example of this phenomenon, China has established clinical research centers with experienced trialists and advanced equipment within major hospitals. To staff these centers, the government has been engaged in an active effort to attract knowledgeable expatriates home. Thus, Western-trained physicians and researchers are

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supplementing the already large (200,000 medical school graduates annually) home-grown talent pool.⁹⁸

For its part, India produces 17,000 physicians and 1,500 new PhDs alongside 500,000 new college graduates with degrees in the life sciences each year. A significant number of Indian natives educated in Western institutions are also returning to the country as their economic options improve.⁹⁹

Starting in 2006, the Drugs Controller General of India implemented a two-track approval system for clinical trials: Category A studies are those with protocols that have been approved by regulators in the U.S., Canada, U.K., Germany, Japan and other countries with advanced review capabilities; these receive expedited (three month) approval. All other trials fall into Category B and undergo the normal (six month) approval process.¹⁰⁰

South Africa first implemented GCP guidelines in 2000 and updated them most recently in 2006. These are in-line with ICH and WHO policies but have been adapted somewhat for the South African context. One measure designed to increase accountability is that the study must include a principal investigator who is resident in the country.¹⁰¹

Ethics committees in Nigeria were “weak or non-existent” a decade ago, according to The Lancet. Since the trovafloxacin trial, however, “a renewed interest by international researchers wishing to work in Nigeria has led to bioethics fellowships and placements in western universities for Nigerian researchers, and more recently programmes have been established within the country. Capacity building initiatives aimed at training bioethicists and researchers have been launched, and two national research ethics training programmes have been undertaken in the past five years, in which more than 100 health researchers and ethics committee members took part.”¹⁰² Further, the Association for Good Clinical Practice in Nigeria (AGCPN), an organization aimed at “expanding the clinical trial infrastructure in Nigeria and creating a forum for clinical research practitioners to exchange ideas on/encourage best practices” has trained more than 350 health professionals since its founding in 2005.¹⁰³ AGCPN is also working to improve the informed consent process, using schematics and translators for patients who may face literacy or language problems.¹⁰⁴

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Clinical trial registries are a leading mechanism for increasing the level of transparency in the research process. Indeed, due to efforts such as the WHO International Clinical Trials Registry Platform and a decision by the International Committee of Medical Journal Editors (ICMJE) to require registration as a precondition for publishing study results, registries are “becoming part of the research paradigm internationally.”¹⁰⁵ Given the heightened safety and ethical concerns associated with trials in developing countries, it is worth noting that several of the emerging research centers are following and, in some cases leading, this new paradigm. For example, the Latin American Clinical Trial Register (Latinrec; www.latinrec.org) was initiated in 2003 and has been offering a searchable database of studies in the region since mid-2006.¹⁰⁶ The Clinical Trials Registry – India (www.ctri.in) was launched in July 2007 and by July 2009 had well over 300 trials registered.¹⁰⁷ The sponsors are also working with ethics committees to make registration a prerequisite for approval.¹⁰⁸ In South Africa, trials must be listed on the South African National Clinical Trials Register (www.sanctr.gov.za) before enrollment begins.

In short, emerging research locations have made enormous strides towards improving their infrastructures and procedures in the last ten to fifteen years. The billions of dollars invested by pharmaceutical companies and CROs have played a vital role in this evolution and are an irreplaceable resource for ensuring that it continues.

Role of Clinical Research Organizations

The value of the global CRO industry has been estimated at between \$15 and \$24 billion¹⁰⁹ with growth rates in the neighborhood of 15% annually.¹¹⁰ As a result of increasing recognition of the value that CROs offer, spending on CROs and other outside research suppliers is expected to grow from 20% of all R&D spending in 2007 to 25% by 2010. Further, this higher level of participation on a relative basis takes place in a context of R&D expenditures that are expected to increase by 50% on an absolute basis between 2005 and 2010.¹¹¹

Reasons for outsourcing R&D include reduced costs, access to additional capacity, consistency of research methods, expertise and technologies, a reduction in fixed costs with a corresponding

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increase in operational flexibility and accelerated development schedules.¹¹² Of these, accelerated development is among the most important considerations. A study by the Tufts Center for the Study of Drug Development survey found that projects which rely heavily on CROs are submitted more than 30 days closer to their projected submission date than those with low CRO usage. Projects were also delivered with levels of quality comparable to in-house work.¹¹³ It is difficult to overstate the importance of delivering quality results on schedule. Consider that for each day that a drug's launch is delayed in clinical trials or the regulatory review process, approximately \$37,000 of additional development costs are tacked on and the lost revenues in the U.S. alone can equal \$23 million.¹¹⁴

CROs have been a leading force in the increasing globalization of clinical research and in the implementation of uniform standards of quality.¹¹⁵ Members of the Association of Clinical Research Organizations (ACRO), which represents the major global CROs, employ nearly 70,000 people, more than half of whom are outside the U.S. In 2008, ACRO member companies conducted more than 9,000 clinical trials globally with research carried out in 115 countries.¹¹⁶

CRO capabilities are especially important in developing countries as their advantages relative to company-run clinical trials may be even more pronounced than in established markets. For example, by maintaining local offices and working across multiple therapeutic categories, CROs allow sponsors to take advantage of existing networks instead of having to duplicate these efforts in each country. Given their experience levels, CROs are more likely to have a deeper understanding of local language, culture and norms, qualities which lead to better relations with investigators and improved trial execution.¹¹⁷

The presence of CROs benefits host countries as well. For example, they provide advanced equipment and trained personnel which are required for the study but are available for use in other aspects of an institution's practice. CROs have also been instrumental in harmonizing research norms in emerging countries with developed world standards.¹¹⁸ This creates a virtuous cycle of knowledge transfer to poor countries and expanded opportunities to conduct research that offers worldwide benefits. In addition, by conducting studies in 115 countries,¹¹⁹ CROs are in many cases providing high paying jobs in areas where employment opportunities are scarce. By relying on pre-existing CRO

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capabilities, trial sponsors are able to move into the clinical testing phase without having to create in-house R&D infrastructure.¹²⁰ This has become increasingly important as biopharmaceutical firms in emerging markets such as South Korea, Taiwan, China and India have begun to move into original drug research within the last few years.

Conclusion

Although legitimate concerns have been raised in the past about clinical trials in emerging countries, the ability to conduct high quality studies in these locations has been enormously improved over the previous ten to fifteen years. The research infrastructures in Central and Eastern European as well as in several East Asian countries, which were among the first emerging areas to participate in trials, are now comparable to those in well-established regions. Countries that began hosting studies more recently are also making rapid progress to ensure that they are able to attract clinical trials and the benefits that trials provide. Biopharmaceutical firms and their CRO partners have played and continue to play a leading role in advancing research capabilities throughout the world.

As we have seen, ethical research norms are global in nature and do not vary from place to place. Further, commercial sponsors have very strong incentives to ensure that their investments in clinical research will be accepted by regulatory agencies in the developed countries where they earn the vast majority of their revenues. Indeed, companies that work exclusively in the clinical research field can easily be forced out of business by market forces that demand strict compliance with these ethical rules.

In light of growing activity in emerging countries, major regulatory agencies have recognized the need for greater oversight of international trials and are responding with a substantial commitment of resources to ensure that all research meets the highest ethical and quality standards. There are now more inspections than in the past and these are taking place at an earlier stage than has traditionally been the case. This is a welcome move that provides yet another level of confidence that studies will yield reliable results while providing a safe environment for patients.

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The advance of medical science is leading to more clinical trials and these trials are increasingly complex, time-consuming and expensive. Restricting the ability of emerging countries to participate in clinical research would add still more expenses and further delay the ability of patients to access new therapies. It would also deny an important source of investment, employment, health care and knowledge transfer to areas that are desperately in need of all these things. Rather than placing further barriers to drug development, efforts should be focused on enhancing the progress that has already been made while continuing to train and monitor researchers throughout the world to ensure their compliance with the highest standards. Fortunately, much of this is already being done as part of the normal business practices of biopharmaceutical companies and CROs, all of whom have a major stake in a strong and improving clinical research environment.

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Appendix A: Estimated Time to Enroll All Open Phase III Cancer Studies in U.S.-only versus Globally

Geography	Line	Statistic	Figure	Source or Calculation
US Only	A	Total Cancer Incidence in US	1,437,180	American Cancer Society 2008
	B	Participation Rate	5%	Industry Statistics
	C	Total Annual Patients Willing to Enroll	71,859	A x B
	D	Number Phase III Cancer Studies in US	481	Clinicaltrials.gov (open Phase III cancer studies)
	E	Patients Willing to Enroll Per Study	149	C / D
	F	Percent Excluded due to Screening Factors	20%	Industry Statistics
	G	Patients Willing and Able to Enroll Per Study	120	E x (1 - F)
	H	Average Patients in a Phase III Cancer Drug Trial	691	VOI Consulting: Label analysis of cancer drugs approved 2006-09
	I	Years Necessary to Fully Enroll all Phase III Cancer Trials with US Patients	5.8	H / G
Global	J	Total Cancer Incidence Worldwide / Male	5,801,839	Globocan 2002
	K	Total Cancer Incidence Worldwide / Female	5,060,657	Globocan 2002
	L	Total Worldwide Cancer Incidence	10,862,496	J + K
	M	Participation Rate	5.0%	Assumes same as US. Conservative estimate.
	N	Total Annual Patients Willing to Enroll	543,125	L x M
	O	Number Phase III Cancer Studies Globally	1,218	Clinicaltrials.gov (open Phase III cancer studies worldwide)
	P	Patients Willing to Enroll Per Study	446	N / O
	Q	Percent Excluded due to Screening Factors	20%	Industry Statistics
	R	Patients Willing and Able to Enroll Per Study	357	P x (1 - Q)
	S	Average Patients in a Phase III Cancer Drug Trial	691	VOI Consulting: Label analysis of cancer drugs approved 2006-09
	T	Years Necessary to Fully Enroll all Phase III Cancer Trials with Global Patients	1.9	S / R
		Difference between US-only and Global Trials (Years)	(3.8)	T - I

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Appendix A: Overview

This appendix provides the methodology used to calculate the previously cited estimates on the time to enroll all currently open Phase III oncology drug trials if studies were restricted to the U.S. as compared to using both U.S. and global sites. The detailed calculations are shown on the previous page.

Appendix A: Methodology

To arrive at the results, VOI Consulting used the annual number of newly diagnosed cancer cases in the U.S. (Cancer Society, 2008) divided by the 5% of patients willing to enroll.¹²¹ This gives the annual potential enrolled patient base (approximately 72,000). Next, we used ClinicalTrials.gov to find the number of ongoing Phase III cancer trials in the U.S. (481 as of April 14, 2009). Dividing the potential patient base by the number of trials gives the average number of patients willing to enroll per study (149). Assuming that 20% of these are excluded for various reasons during the screening process, the result is 120 patients willing and able to enroll per study.

As with the U.S., the top-line of the global estimate contains the number of total cancer cases diagnosed in a year. The source for the worldwide data is the Globocan 2002 estimates maintained by the International Agency for Cancer Research (<http://www-dep.iarc.fr>). This is the closest available source to the U.S. figures provided by the American Cancer Society.

For the global participation rate, we used the same (5%) figure as in the U.S. Although this is almost certainly a conservative estimate, it is consistent across geographies – in other words, we use the same approach to arrive at the U.S. and global figures.

Line O in the global estimates reflects the total number of Phase III cancer trials listed on clinicaltrials.gov that are taking place anywhere in the world. This is a higher number than used in the section for U.S. estimates (1,218 versus 481) and reflects the fact that ex-U.S. studies would face competition for patients from trials already underway in these countries.

To determine the average size of a Phase III cancer drug trial, we looked at the prescribing labels of cancer drugs approved in the U.S. between January 2006 and March 2009. This yielded an average figure of 691 patients per Phase III trial.

By dividing the 691 average patients per Phase III drug trial by the 120 U.S. patients willing and able to participate per study per year, we arrive at the bottom line result – i.e. that it would take 5.8 years to fully enroll the currently

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ongoing studies using U.S. patients alone ($691 / 120 = 5.76$). Replacing the U.S. number in the denominator with the global figure of 357 patients willing and able to participate per study per year indicates that it would require 1.9 years to fully enroll all Phase III trials currently underway around the world. Parenthetically, the bottom line results are highly sensitive to the participation rate figure: for example, if 10% of patients participated on a global basis, the time to complete all Phase III studies would drop to one year.

There are some limitations to this methodology. For example, we used all cancer Phase III studies (including academic, government sponsored, drug, etc) to determine how many patients were available per trial but used the average size of a Phase III trial aimed at drug approval as the measurement for the average enrollment objective. In reality, non-drug Phase III trials are likely to be significantly smaller than drug approval trials. We chose to use this approach because drug trials compete for patients against all trials – not just other drug trials.

Also, we used the number of newly diagnosed cancer patients (i.e. incidence) as the starting point for the overall patient population size. Some might argue that this should be the total number of patients living and ever diagnosed with cancer (i.e. prevalence). Our rationale here is that cancer is a particularly aggressive disease that is likely to be treated at or near the time of diagnosis. Since there has been a high level of clinical trial activity in this area for years, most patients who are willing and able to enroll in a trial would likely do so around the time they start treatment. Therefore, we can say with reasonable confidence that the number of newly diagnosed cancer patients is the relevant measurement for how many newly available clinical trial participants could be expected to join trials in a year.

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About VOI Consulting, Inc.

Founded in 1998, VOI Consulting is a life sciences advisory and publishing company dedicated to providing pharmaceutical and biopharmaceutical clients with fact-based analysis and business intelligence to meet market challenges in today's highly competitive global environment. By skillfully employing innovative research techniques and advanced analytical tools VOI's services help clients minimize risks, cut costs and maximize commercial opportunities.

VOI Consulting's services are global in reach, are relevant for any therapeutic category and span the entire range of the pharmaceutical lifecycle. Whether clients are planning a clinical trial or need to assess the market for a generic drug, whether they operate in developed countries or are looking at emerging world opportunities, VOI helps them execute better, faster and cheaper.

In addition to its strategic advisory services, Value of Insight Consulting (VOI) has published many dozen books, articles, reports and reference guides for the life sciences field. In particular, our annual publications, *PharmaHandbook: A Guide to the International Pharmaceutical Industry* and *GenericHandbook: A Guide to the US Multisource Drug Industry*, have become the standard resources on their respective topics with customers in more than 45 countries and highly favorable reviews in the business and academic press.

About the Author

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