

CONTRACT RESEARCH ORGANIZATIONS: AN INDUSTRY ANALYSIS

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CONTRACT RESEARCH ORGANIZATIONS: AN INDUSTRY ANALYSIS ABSTRACT

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Purpose

U.S. pharmaceutical companies outsource research activities to contract research organizations (CROs) to increase their profit margins and better position themselves in the rapidly-changing healthcare environment. In this article, the authors explore the evolution of the CRO industry in the United States and worldwide, and discuss the benefits and pitfalls of CRO globalization in recent years.

Design/methodology approach

The organizational ecology framework is used to analyze the CROs' emergence, growth, and evolution to date, in response to environmental changes. Organizational ecology is the study of dynamic changes within a given set of organizations. Most organizations have structural inertia that hinders adaptation when the environment changes. Those organizations that become incompatible with the environment are eventually replaced through competition with new organizations better suited to external demands

Findings

In recent years, there has been a clear shift toward globalization of clinical trials, as a result of the economic downturn, tighter control in the US and less stringent regulations abroad, in addition to a quest to increase efficiency, cost savings, and greater access to diverse study populations. The areas in most demand to conduct clinical trials in are India, China, and Central

and Eastern Europe. Conducting clinical trials in developing countries can be beneficial in that it could stimulate research collaborations and could introduce new drugs throughout the world. At the same time, there is concern about the accuracy and quality of clinical trial data, as well as the ethical treatment and safety of research participants in the absence of strict research monitoring. A multi-level approach could be used to address these concerns.

Originality/value

This article gives a contemporary overview of the CRO industry. The authors explain its current state within an organizational change framework. The activities of CROs in the United States are compared and contrasted to those in emerging markets. The implications of research outsourcing and CRO globalization are discussed.

Keywords: Contract Research Organizations, CROs, CRO General Review, CRO Globalization, Drug Development, FDA, CRO Market Analysis

Contract Research Organizations: An Industry Analysis

Introduction

A number of factors create a high demand for clinical trials in the United States. Some of these factors are the aging of the population, the high prevalence of chronic diseases, the embrace by physicians and payers of evidence-based medicine, and the patients' common belief that they will benefit from new medical technologies and treatments. Patients volunteer into clinical trials to gain early access to medication, treatments, and medical care. A large number of Americans (70%-83%) believe that clinical research is "very important" or "essential" to advancing public health (Research America, 2009). However, only a minority of Americans (31%) believes that the United States Food and Drug Administration (FDA) has been effective at ensuring public and patient safety (Harris Interactive, 2007), despite FDA's mission to promote and protect public health by approving safe and effective drugs.

Several challenges have faced the drug industry: rising drug costs, differences in cost between drugs in the United States and in other developed countries such as Canada and the United Kingdom, and long marketing time. Furthermore, the safety of drug development has been called into question and public trust in the industry has declined (Glickman *et al.*, 2009; Shtilman, 2009).

In recent years, the drug industry has had to change the way drugs are developed in order to ensure better patient safety. The quest for reliable endpoints in research has led to a large number of trials. As of October 2011, more than 114,000 clinical trials were being conducted in the U.S. and other 177 countries (National Institutes of Health, 2011). An estimated 900 new drugs and vaccines targeting 100 diseases are in development in the U.S., either in clinical trials or under FDA review (PhRMA, 2011).

Clinical trials have shifted from academic medical centers to community-based practices (Robuck and Wurzelmann, 2005; Scott, 2003). Community-based sites could be a single community hospital or physician groups (solo practice, small group, medium site group, large single specialty, or multi-specialty group). In addition, greater FDA scrutiny, complicated logistics, and requirements for more data have helped the growth in professional research sites. Currently, pharmaceutical and biotechnology companies increasingly use contract research organizations (CROs) to complete drug research projects faster and at a lower cost. The CRO market size was estimated at \$24 billion in 2010 and increasing by approximately 15%, despite the fact that major CROs have seen their profits fall by 50% compared to previous years (Biopharm Knowledge Publishing, 2011).

This article uses the organizational ecology framework (Hannan and Freeman, 1977; Ivery, 2007) to analyze the lifecycle of CROs in response to their environment: their birth, growth, and evolution up to the current stage. The paper will first discuss the drug development process, the role of CROs, and outsourcing in clinical research. Second, the paper will include an analysis of the CRO industry, how it evolved over time, the different factors affecting it, the current globalization stage, and the positive and negative consequences of globalization. Subsequent articles by the same authors will analyze the effects of research outsourcing on the cost and quality of clinical trials conducted by CROs and the use of CROs by nonprofit and for-profit U.S. community-based hospitals.

Drug development process

It is essential to understand the long and complex drug development process in the U.S. before analyzing the role of CROs. In 1938 the Food, Drug, and Cosmetic Act was passed to ensure that

every new drug is approved by the United States Food and Drug Administration (FDA) before it is available on the market. The drug development process is induced by both a medical need and a business opportunity. The pharmaceutical industry invests as much as five times more than the average manufacturing company in research and development relative to their sales (Congressional Budget Office, 2006). Globally, the U.S. represents the largest market for pharmaceuticals, accounting for approximately \$190.4 billion in 2005 compared to \$57.5 billion in Japan (Matrix 2.0, 2006). Creating a new drug is both time consuming and expensive. In 2005, the average cost of developing drugs was estimated at \$1.3 billion (DiMasi and Grabowski, 2007).

Drug research and development process

The research and development (R&D) process of every new drug is complex and lengthy. There are four stages in the process: drug discovery, preclinical research, clinical trials, and FDA review. The time span between the drug discovery phase and the FDA approval can take up to 15 years (PhRMA, 2011b). On average, for every product that will eventually reach the market, 10,000 compounds are screened during the discovery stage. During this stage, drugs are studied in-vitro and, if possible, in animal models of disease. Approximately 250 compounds make it into stage 2 of drug development, known as preclinical research, where pharmacology and toxicology studies are conducted. If the results in stage 2 look promising, the manufacturer submits an Investigational New Drug (IND) application to the FDA for review. If the application is approved, the manufacturer may proceed with clinical testing (stage 3) in humans. About five compounds are approved for stage 3 clinical trials, during which they are tested on volunteer participants in three phases. This stage can take up to seven years to complete (PhRMA, 2011b).

Types of clinical trials (stage 3)

The aim of phase I of clinical trials is to establish the safety and pharmacology of the drug. Phase I is conducted with 20 to 80 healthy volunteers who are closely monitored in an in-patient setting. This trial period may take up to two years.

In phase II of clinical trials, research focuses on pharmacokinetics, bioavailability, drug-disease, and drug-drug interactions. The intent is to test the effectiveness of drugs on specific populations and for specific diseases. This phase may involve between 100-500 subjects over longer treatment intervals (between six and 12 weeks).

The main aim behind phase III of clinical trials is to confirm the safety and efficacy of the drug under study. The experimental drug or treatment is given to large groups of volunteer subjects (between 1,000-5,000 participants) in the U.S. and other countries. The FDA requires at least two “adequate and well-controlled studies” for approval (PhRMA, 2011a; PhRMA, 2011b).

FDA review

Once phase III of the clinical trials is completed successfully, the manufacturing company files a New Drug Application (NDA) with the FDA. This application includes all the drug-related information collected in the previous steps. The review takes place in stage 4 of the drug development process and may take up to two years. A drug may get an “S” for standard review if it is similar to other drugs currently available, or a “P” for priority review if the drug represents a significant advance over existing products. All drugs must be approved by the FDA before they could be marketed to consumers (Madden, 2005).

The FDA could approve drugs conditionally and request the manufacturer to continue to perform further studies. Those extended studies are called phase IV or commitment studies. Phase IV studies are used to confirm the drug’s safety and efficacy, as well as to test for side

effects and additional benefits. In theory, failure to complete such studies should result in the drug's withdrawal from the U.S. market. However, according to the FDA's 2005 report on performance of the commitment studies, of 1,191 open post-marketing commitment studies, only 114 had been conducted (Madden, 2005). Daniel Klein and Alexander Tabarrok argue that "FDA control over drugs and devices has often overlooked costs that almost certainly exceed the benefits" (Madden, 2005). They believe the FDA regulation of the medical industry has suppressed and delayed new drugs and devices. Furthermore, the FDA's review process has increased costs, with a net result of more morbidity and mortality.

Outsourcing in clinical research

Large pharmaceutical companies increasingly are using "downsizing" strategies to be able to concentrate their resources on core skills and specialties. Pharmaceutical companies are outsourcing aspects of their drug development, manufacturing, and marketing processes. There are several reasons behind this outsourcing process, some of which include lack of in-house capacity, skill deficiency, and cost control. For example, specific services may be unavailable in a pharmaceutical company. The company may need special regulatory expertise to operate in a foreign country, or the company may want to reduce its fixed cost and turn part of it into variable cost. However, one of the main reasons for outsourcing is the downward cost pressures exerted on pharmaceutical manufacturers' profit margins. Given that these cost pressures may continue to increase in the future, contract research organizations (CROs) are becoming more of an important strategic partner for pharmaceutical companies.

CROs' role

According to the Code of Federal Regulations, the U.S. FDA regulations state that a CRO is "a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration" (US Food and Drug Administration, 2011).

When CROs were first created, they offered pharmaceutical companies a limited number of research services. Outsourcing activities included either biostatistician consulting or clinical research associate (person responsible for monitoring investigational sites for regulatory compliance) support (Beach, 2001). All those activities were moderately specialized. At present, full-service CROs offer a broader range of services including the selection of investigators and investigational sites, assistance with patient recruitment, safety surveillance and reporting, site audits, and clinical trials data management and biostatistics (Getz and Vogel, 2009; Shtilman, 2009).

Organizational ecology theory and CROs

Organizational ecology is the study of dynamic changes within a given set of organizations. It examines the birth and mortality of organizations and organizational forms within the population over long periods. Most organizations have structural inertia that hinders adaptation when the environment changes. Those organizations that become incompatible with the environment are eventually replaced through competition with new organizations better suited to external demands (Hannan and Freeman, 1977; Ivery, 2007). T.Y. Lee, Vice President of Clinical Development and Asia Venture of Kendle International stated, "The traditional nature of CROs has changed and they will evolve into a formidable industry" (Lee, 1998). Based on the

organizational ecology theory, the following section of this article discusses the evolution of CROs over time.

Birth period

Pharmaceutical companies faced a number of pressures between 1970 and early 1990s. The R&D cost was doubling every five years. The average cost of bringing a drug to market grew from \$125 million in 1989 to \$231 million in 1993 (Brooks, 2006). Although prescription drug prices continued to rise, the probability of developing a successful drug was very small. In addition, the R&D costs increased faster than drug prices. Furthermore, biotech companies were faced with decreasing available capital. The industry's stock value fell 6%, while the R&D rose about 14% (Brooks, 2006). Several important changes occurred: downsizing of pharmaceutical companies, out-licensing non major products, and a number of mergers and consolidations (Lee, 1998). Other pharmaceutical companies developed the over-the-counter market and some simply gave up research and clinical trials.

As a result of these changes, CROs were born to fill a demand for innovative organizations whose routines and competencies vary from the pharmaceutical companies. CROs were successful in reproducing themselves and giving rise to a new population of organizations.

Growth period

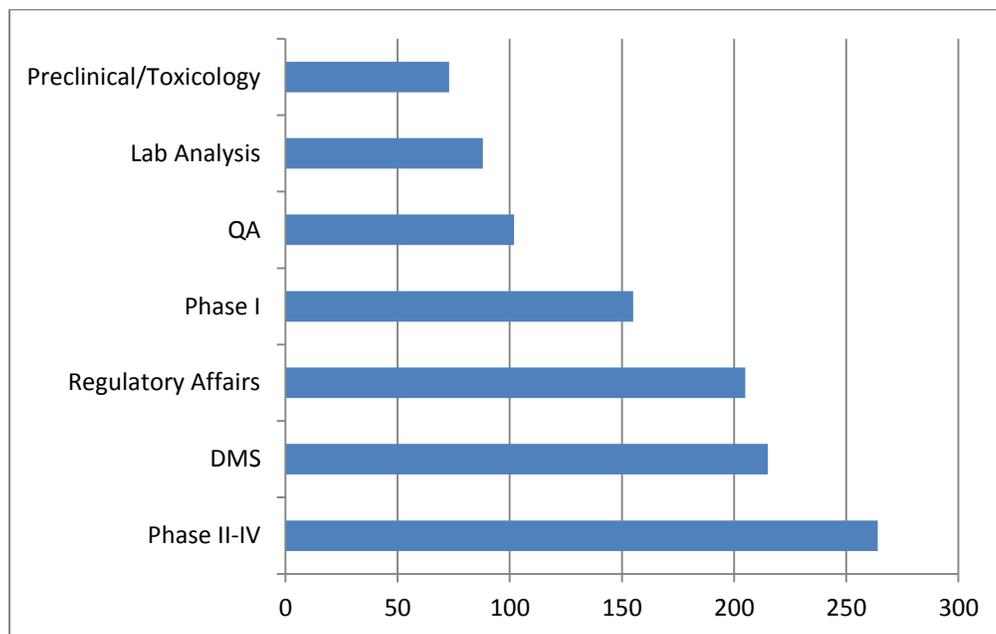
The CRO population gradually increased. In 2004, top CROs managed about 23,000 phase I through phase IV trials worldwide, monitored more than 150,000 clinical investigators, and enrolled more than 640,000 new subjects (Brooks, 2006). The main reason behind this growth is CROs' specialization and the creation of niche CRO service providers. Today, the industry is evolving more toward a full-service model, with CROs offering services from the earliest stages

of development through clinical trials and post-approval research. CenterWatch surveys of major pharmaceutical companies revealed that sponsor outsourcing activities have changed in recent years (CenterWatch, 2009). Sponsors are not increasing the overall level of CRO involvement in their clinical projects; instead, they are using CROs for a variety of clinical activities.

CROs in North America offer a wide range of services, as illustrated in Figure 1. As of 2006, most services were being offered in phase II through phase IV trials, followed by Dealer Management Systems (DMS), and regulatory affairs.

Figure 1

Services Offered by CROs in North America (2006)



Source: Biopharm Knowledge Publishing, The Contract Research Annual Review 2006

Because CROs are evolving toward full-service companies, they are increasingly assuming the regulatory and ethical risks and responsibilities inherent in the conduct of clinical trials. In this full-service role, CROs, unlike sponsors, have no vested interest in the outcome of the study. However, like sponsors, they are subject to heavy regulation by the federal

government (Glickman *et al.*, 2009; Shtilman, 2009). CROs must follow state laws and international guidelines, as well as their own operating procedures. CROs are also subject to comprehensive audits by the FDA and the sponsoring companies.

Current period

CROs pursue different strategies to overcome the pressures discussed above. Full-service CROs are getting competition from nimble niche and midsize players. To overcome the competition, those organizations tend to operate like their focused and niche-oriented clinical service counterparts. As for the mid-sized, small, and niche CROs, their aim is to maintain growth. Thus, these organizations mainly focus on those services that have secured their relationships with sponsors. One could call this phase a renaissance of the CRO market, in which study sponsors are increasingly dependent upon research outsourcing.

CRO globalization and emerging markets

The pharmaceutical industry has been increasingly challenged to expedite the drug development process and to make it more efficient. Competition, poor economic conditions, downsizing, increased government scrutiny, and pricing pressure from healthcare organizations have lead pharmaceutical companies to find ways to reduce the costs of production and manufacturing (Gad and Spainhour, 2011).

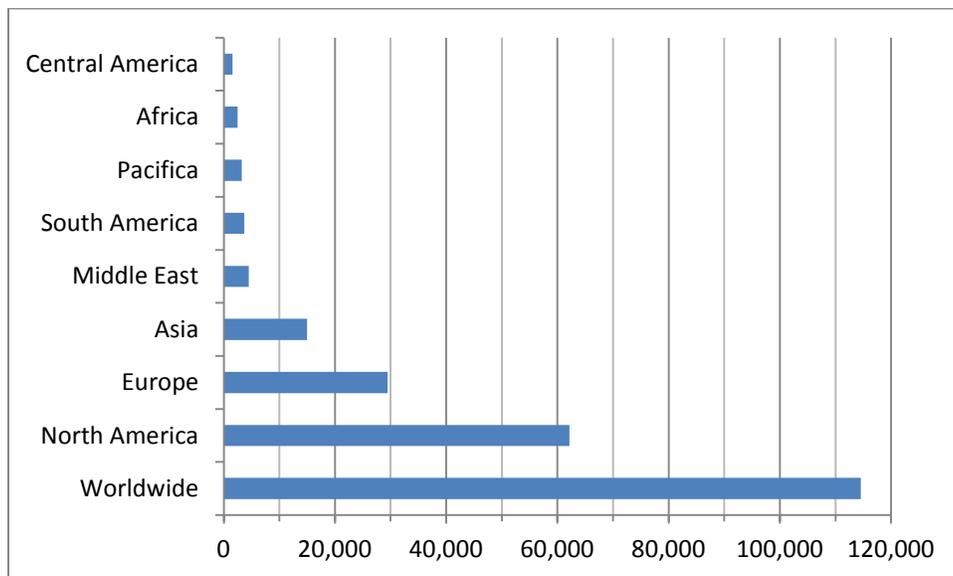
Most pharmaceutical research has traditionally been conducted in affluent regions such as North America, Western Europe, and Australia; these three regions in 2007 held 66% of the clinical trial market share, with the U.S. hosting 49% of trial sites. However, other regions have emerged in recent years (Thiers *et al.*, 2008). Reasons for this globalization trend have included:

reduced operational costs; ability to recruit more diverse research participants in a shorter amount of time; easier regulatory processes abroad; faster protocol approval; and availability of highly skilled professionals in emerging research markets (Clemens, 2010; Singh, 2008; Thiers *et al.*, 2008).

This influx and geographical spread of U.S.-sponsored clinical trials is being summarized in a data registry, Clinicaltrials.gov, which includes detailed information about completed and ongoing trials in 177 countries. Figure 2 indicates the number of clinical trials (all phases) being conducted in different regions of the world by US companies and registered with the National Institutes of Health as of October 2011 (US National Institutes of Health, 2011).

FIGURE 2

Number of Clinical Trials by World Regions (2011)



Source: US National Institutes of Health, ClinicalTrials.gov registry (2011)

Table 1 displays the countries where most trials documented in the registry are being conducted (US National Institutes of Health, 2011).

TABLE 1

Number of Clinical Trials by Country (2011)

Country	Number of Clinical Trials
United States	56,981
Canada	8,745
Germany	8,002
France	6,820
United Kingdom	5,867
Italy	4,461
Spain	3,920
Netherlands	3,635
Belgium	3,378
Israel	3,190
Australia	3,049
South Korea	2,800
Denmark	2,799
China	2,460
Brazil	2,448
Poland	2,405
Switzerland	2,376
Taiwan	2,341
Sweden	2,320
Austria	2,125
Japan	2,014

Source: US National Institutes of Health, ClinicalTrials.gov registry (2011). Only countries conducting 2,000 or more clinical trials were included in the table.

Operating in different countries poses problems to the CROs, as well as to the sponsoring companies, because they are subject to different guidelines and regulations, both national and international (Premkumar *et al.*, 2010). To address some of the problems, the Global CRO Council for Bioanalysis was created by 34 CROs in 2010 (Global CRO Council, n.d.).

The outsourcing of clinical trials to developing countries has not been without controversy. Proponents discuss the financial benefits brought to the country, as well as the medical care that study volunteers receive at no expense to them. Critics, however, point out that the research subjects typically lack health insurance and financial means to receive medical care on their own. Therefore, economic reasons are forcing them to become test subjects, though sometimes they are not informed they are being tested and being administered drugs that have not yet been approved (Clemens, 2010; Drabu *et al.*, 2010; Singh, 2008). Some credibility concerns should be alleviated by CROs joining international regulatory bodies. For example, numerous CROs have been found in compliance with Good Laboratory Practices (GLP) developed by the Organization for Economic Cooperation and Development (OECD) (Gad and Spainhour, 2011).

In recent years, three regions have emerged as “hot” up-and-coming CRO markets: India, China, and Central and Eastern Europe. The following paragraphs discuss the rise of these new CRO markets and their advantages over traditional clinical research sites.

CROs in India

For Pai *et al.*(2009), it is the “six senses” that are the driving forces behind India’s emergence as a CRO market: patient recruitment rates, quality of services, reasonable cost-quality ratio, existence of regulatory agencies, high standards of care, and English-speaking skills. The FDA

has even opened a regional office there, as a result of the volume of data generated in clinical trials (Pai *et al.*, 2009). International companies are entering the healthcare sector and creating their own niches (Drabu *et al.*, 2010). The cost of conducting clinical trials in India is estimated to be 50%-60% lower than in the United States or the European Union (Bhowmik *et al.*, 2010).

Estimates put India's CRO market at \$35 billion by 2013 (Drabu *et al.*, 2010). Local market regulations continue to make India more and more appealing to pharmaceutical companies. The Indian customs department has eliminated import taxes for investigational drugs (Pai *et al.*, 2009). All Indian clinical trials must be registered in the Clinical Trials Registry - India before volunteer enrollment can proceed (Drabu *et al.*, 2010).

In spite of India's increased visibility in the CRO market, the economic downturn has taken a toll. Some CROs have ceased operations (particularly those with a few clients and a few projects), while others continue to expand. One Indian CRO executive saw the recession in the U.S. as an opportunity to attract and hire Indian-born, U.S.-educated physicians and scientists (Jayaraman, 2009).

Some are beginning to wonder whether India's CRO potential has really lived up to the hype (Redfearn, 2011). The number of clinical trials outsourced to India has been declining recently and commentators see several possible explanations: the Western pharmaceutical industry entered the Indian market too quickly, too soon, without plans for long-term investments; Western companies' "one size fits all" approach to research does not work in India; CROs started charging study sponsors Western prices, despite the Indian market being much less expensive; bureaucratic regulatory process and random policies imposed on CROs (Redfearn, 2011).

CROs in China

China's CRO market developed in the early 2000s, after the country joined the World Trade Organization and developed regulations for the drug industry. Novo Nordisk set up an R&D center there in 2002 and other large U.S. pharmaceutical companies followed in subsequent years. It is estimated that China will soon be the second largest Asian pharmaceutical market after Japan (Gambrill, 2010). CRO revenues in China are forecast to reach \$240 million by 2012 (Gad and Spainhour, 2011). Although there has been some suspicion over the quality and validity of clinical trials conducted by Chinese CROs, there does not appear to be any convincing evidence to prove wrongdoing (Gad and Spainhour, 2011). As with India, the FDA now has permanent offices in China.

Some downsides to conducting clinical trials in China are said to include: slow turnaround, language barriers, and government interference in the regulatory process. One senior director at a U.S. pharmaceutical company thinks, "[P]eople are taking a wait-and-see approach to China. There's a fear of getting it wrong. People are instead working to understand the marketplace, the legal infrastructure, the IP rights" (Redfearn, 2011, p. 22).

CROs in Central and Eastern Europe

A different picture emerges from Europe. More than one in four clinical trials documented in NIH's registry is being conducted in Europe (US National Institutes of Health, 2011). CRO revenues are forecast to increase to \$7.6 billion in 2012 (Newman, 2010). There has been an increase in the number of niche CROs in regulatory, pharmacovigilance, and clinical drug supply, while other large CROs are struggling.

Europe is a desirable market for pharmaceutical companies to conduct trials, particularly phase I, for different reasons than emerging countries: highly qualified staff, fluency in foreign languages, quality of services and infrastructure, size of the continent, and ability to handle multi-country trials (Newman, 2010; Shtilman, 2009). The main deterrent, however, is the cost of conducting the trials. In fact, the overall costs in the European Union (including taxes, salaries, overhead, etc.) are said to be higher than those in the U.S. (Newman, 2010). One way European CROs are coping with the difficult economic situation worldwide is by developing strategic alliances and expanding to cheaper, less saturated markets in Eastern Europe (Newman, 2010).

The former Soviet Union countries are particularly appealing to large pharmaceutical companies for some of the reasons mentioned above (Shtilman, 2009). However, the expansion of clinical trials in that area has also led to ethical concerns for the safety and protection of research subjects. The FDA, although it oversees all clinical research conducted by U.S. companies and their CROs, has effective jurisdiction only when trials are conducted in the United States. FDA regulations can be circumvented in clinical trials conducted in other countries. Moreover, the governments and regulatory agencies in those countries do not have the knowledge or the capacity to regulate clinical trials and to ensure the safety and ethical treatment of volunteer subjects.

Conclusion

This article used the organizational ecology framework to analyze the lifecycle of CROs: their birth, growth, evolution, and current stage. The paper discussed the drug development process, the role of CROs, outsourcing in clinical research, and the state of the CRO industry. In recent years, there has been a clear shift toward globalization of clinical trials, as a result of the

economic downturn, tighter control in the US and less stringent regulations abroad, and in a quest for more efficiency, cost savings, and greater access to diverse study populations (Glickman *et al.*, 2009).

The article has identified some of the positive and negative consequences of globalization. Conducting clinical trials in developing countries can be beneficial in that it could stimulate research collaborations and could introduce new drugs throughout the world. At the same time, there is concern about the accuracy and quality of clinical trial data, as well as the ethical treatment and safety of research participants in the absence of strict research monitoring (Glickman *et al.*, 2009; Shtilman, 2009). It has been suggested that multiple approaches are needed to alleviate these concerns. The approaches could involve policy changes in the countries where clinical trials are conducted; tighter control and authority to enforce research regulations; mandating the use of Institutional Review Boards (IRBs); conducting research to address local societal needs rather than one company's interest; transparency in the conduct of research and the results obtained; education of volunteer participants about the research process and its possible consequences (Glickman *et al.*, 2009).

As clinical trials and research outsourcing continue to expand to less developed countries, more challenges are likely to come up. Subsequent articles by these authors will focus on the effects of research outsourcing on the quality and the cost of clinical trials conducted by CROs.

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