Clinical Research Opportunities

What You Need to Know for Your Practice

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Cardiologists and cardiovascular practitioners are facing significant reimbursement constraints. In this setting, increasing numbers of practitioners are looking to participate in clinical research as a new source of revenue. An aging population and consolidation among pharmaceutical companies, medical device companies, and contract research organizations are placing great emphasis on speed of new products to market. Opportunities exist for well-positioned and knowledgeable clinical investigators to enhance their practices, increase their professional knowledge, and expand their network of scientific colleagues. This article provides an overview of the drug and pharmaceutical industry referable to clinical investigation, the tools necessary to become a valued, principal investigator and an outline of challenges and opportunities for clinicians wishing to engage and enhance their clinical research activities.

Many cardiologists and cardiovascular surgeons facing decreasing reimbursement (stemming from the prevalence of managed care and the ramifications of the Balanced Budget Act) are seeking other sources of revenue. For some practitioners, clinical research might represent an exciting opportunity. In 1998, research-based pharmaceutical companies spent 15.8% of research and development (R & D) expenditures on drugs acting on the cardiovascular system. If research-based pharmaceutical companies continue to invest the same share in 2000, an estimated $4.1 billion will be spent on cardiovascular drug research.1 (See Figure 1 for a comparison of estimated R&D expenditures by product class for 2000.) As of March 1999, 315 cardiovascular drugs were in clinical trials worldwide (phases I-III) and 492 in preclinical studies.2

But how should practitioners evaluate whether clinical research makes sense for themselves and their practices? In this article, we provide a framework for evaluating opportunities to participate in clinical research. In Section I, we present an overview of the drug and pharmaceutical industry including its growth and challenges, the increasing role of contract research organizations (CROs), profile of investigators and future trends. In Section II, we discuss issues that physicians need to consider before becoming involved in clinical research. The final two sections identify opportunities and outline initial steps for involvement in this segment of the healthcare industry.

SECTION I: OVERVIEW OF DRUG AND PHARMACEUTICAL INDUSTRY

Growth and Challenges

There is no arguing that pharmaceutical companies are investing more money in drug R & D. In 2000, research-based pharmaceutical companies (both US-owned and foreign-owned) will invest an estimated $22.5 billion in R & D within the United States—an 11.8% increase from 1999 and an 89.3% increase from 1995. US-owned research-based pharmaceutical companies will invest an estimated $4.0 billion abroad, a 1.2% increase from 1999 and a 19.1% increase from 1995.1

Another indicator of growth is the increase in R & D expenditures measured as a percentage of drug sales. An estimated 20.3% of drug sales will be spent on R & D in 2000, up from 16.2% in 1990. In the United States, approximately one-third of pharmaceutical R & D is spent on the evaluation of investigational new drugs in human clinical trials.3

With all the investment in R&D, drug companies face real challenges, such as the time and costs required to bring a new drug to market. This is exacerbated by the fact that on average, only 20% of drugs that start clinical development are ultimately approved for marketing.2 According to the Tufts Center for the Study of Drug Development, cardiovascular drugs approved in 1996 to 1998 took an average 7.3 years to go through the clinical and approval phases of the drug development process.3 Recent estimates on the cost of developing new drugs range from $359 million in 1990 dollars to $608 million in 1996 dollars.2 A statistic frequently quoted is that a drug company loses $1 million each day a drug is not on the market.4

The Bernoulli Principle is a good analogy of these challenges. Figure 2 illustrates how regulation requirements, study design, patient and investigator recruitment, data collection, and reporting all contribute to a bottlenecks of the drug development process. Therel
fore, to expedite an investigational new drug (IND) through the pipeline a drug company needs to produce a higher volume of safety and drug efficacy data faster and at a lower cost.6

One tactic drug companies have pursued is to outsource components of the drug developmental process to CROs.

Increasing Role of CROs

A CRO is an entity that performs research functions on an outsourced basis for drug sponsors, such as clinical program management, protocol development, case reporting, investigator and site recruitment, study monitoring, data management, pharmacoeconomic analysis, and regulatory reporting. A recent survey of pharmaceutical companies by CenterWatch, an industry publication, found that drug sponsors plan to hire CROs “for a significant role” in 65% of drug development projects, up from 60% in 1997 and 28% in 1993.2 CenterWatch also projects that 23% of global pharmaceutical research spending (approximately $4 billion) will be outsourced in 1999, an increase from 21% (approximately $3 billion) in 1998.2

By outsourcing parts of the drug development process, drug companies can shift the fixed costs of maintaining a specialized staff and equipment to CROs. But most importantly, a CRO’s focus, expertise, and experience provide an opportunity to improve productivity and compress the drug development process. The Barnett International Benchmarking Group found that for their clients, CROs had significantly shorter Phase III cycle times than drug sponsors.2 Figure 3 compares the CROs’ and drug sponsors’ Phase III cycle times.

To meet the needs of drug companies, CROs are employing many strategies. Some are positioning themselves to be full-service companies offering the spectrum of services, from study design to regulatory reporting. As with many industries, mergers and acquisitions are helping to increase company size and growth. Since 1996, the top eight CROs have made 37 acquisitions.7 Many CROs, conversely, are realizing that to stay competitive they need to become experts in a “niche” market, i.e., a certain disease or pathology (e.g., cardiology or oncology) or in different phases of drug development (e.g., phase III or IV).

Driven by the ongoing challenge of patient recruitment and the establishment of the International Conference on Harmonization guidelines (which standardize how study information is gathered and reported in the United States, Japan, and the European Union), some CROs are developing capabilities to run clinical trials outside of the United States. With the United States encompassing only 4% of the world’s population, international clinical trials represent an opportunity (albeit with its own set of challenges) to decrease the time and costs to bring a drug to market.7 DataEdge LLC (a US-based company that provides databases of investigators’ costs, CRO capabilities, and study timings) reports that approximately 25% of phase III protocols are multinational and expects the number to rise.8

Profile of Investigators

Physicians who participate in clinical trials are commonly referred to as investigators. Although this terminology implies a background in medical research and academics, more office-based physicians are becoming involved in clinical trials.9 Indeed, fewer first-time investigators come directly from academic hospitals and medical schools, and fewer are classical researchers. Before 1989, 25% of first-time investigators had this background; in 1995 it had dropped to 11%.9 This can be explained partly by the need for patients. Office-based physicians are more likely to have larger patient bases from which to draw than do physicians focused on medical research/teaching.

However, participating in clinical trials requires a significant amount of time and effort from the physician and supporting staff. It is, therefore, not surprising that investigators tend to be more experienced than the overall physician population as measured by year of medical graduation (and probably have more established practices); and are more likely than mainstream physicians to work in group practices and less likely to work in one- or two-physician practices.9

The majority of US investigators, as shown in Figure 4, have participated in only one study during the 7-year period from 1988 to 1995.2,9 This low reengagement rate of investigators suggests many things: 1) investigators underestimated the time and effort required to participate in a clinical trial and decided not to participate in another study; 2) investigators were not chosen again because of poor
performance; 3) the investigator recruitment process is inefficient.  

**Future Trends**

Expect the growth in drug R & D to continue to be fueled by such factors as the aging population, advances in technology, and the exploration of the human genome. Also expect drug companies to increase their use of outsourced clinical trial services. Growth in the CRO industry, however, will likely be uneven.

First of all, the landscape of the CRO industry is changing. Some CROs are merging to become full-service shops. Others are positioning themselves to be niche players. International clinical trials are on the rise. Also, the drug industry can be cyclical. Investigational new drugs placed in the developmental pipeline are not only a function of demand, but also depend on which compounds are discovered. And what if CROs decide to expand into drug discovery to capture some of the profits?

Another trend is the on-going challenge of patient recruitment, which some industry experts claim is the most difficult and time consuming aspect of drug development. This is compounded (as indicated in Figure 5) by an increase in the average number of patients needed per new drug application. Although international clinical trials provide an opportunity to tap into larger patient populations, there are significant hurdles. Development, standardization, and management of international clinical trials become more complicated when countries differ in organization, language, and business and clinical practice culture. There also are ethical issues. For example, is it ethical to have clinical trials in a country that in turn could not afford the drug if it is approved? In the United States, potential investigators need to find a way to market their primary asset—their patient base—to CROs and drug companies. One possibility is for physicians to align with site management organizations (SMOs), which specialize in recruiting patients and moving them through the clinical trials. Figure 6 shows that SMOs’ share of the pharmaceutical and biotechnology industry’s spending on clinical investigators has been increasing.

Lastly, we foresee a continued need for development of a more systematic process to select and recruit investigators. This is especially important as more office-based physicians become involved. Whereas most medical research and teaching take place in 300+ US medical schools, office-based and hospital-employed physicians are found at 7,500+ hospitals and 21,500+ physician group practices. Better selection of investigators is essential to compressing the development cycle.

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**Figure 3.** Phase III cycle times: contract research organization vs sponsor cycle times. Source: Barnett International Benchmarking Corp.; PAREXEL’s Pharmaceutical R & D Statistical Sourcebook, 1999:94.

**Figure 4.** Relative experience of clinical investigators. Source: ACRP white paper on future trends, and Steven M. Rausher, Pharmamillennium ‘99; PAREXEL’s Pharmaceutical R & D Sourcebook, 1999:80.

patient that completes the study, and sometimes receive partial payment for patients that do not complete the study. Fees can vary from a few hundred to thousands of dollars per patient.\textsuperscript{13} The range of these stipends is directly dependent on the physician’s level of involvement in the study. Factors that can affect compensation include length of case report, amount of intervention, out-of-pocket expenses, and depth of coordination.

Because there is no guarantee that research will be profitable, many investigators get involved for other reasons. Participation can often provide access to new technologies and drugs, thus improving patient care. Physicians often enter research simply to modify their daily routine and try something new or add prestige to their practice image.

Numerous factors can impact the success and experience of a clinical study. Investigator success factors would include: willingness to spend time; strict following of protocol; proper and complete answering of all questions on the case report form; supportive infrastructure (at the investigator practice and clinical study coordinator levels); appropriate patient population; and absence of sloppiness in performing research (e.g., data entry, source documentation, and consistent following of protocol).\textsuperscript{13} None of these factors are independent of each other, and inadequacy in one can undermine the validity of the whole study. Even in situations where the physician has carefully followed precise protocols for a study, the results can be skewed if the data are entered incorrectly or the case coordinator has recruited ineligible patients. Patient recruitment is a major strain on time. A qualified case coordinator can not only aid in recruiting patients, but also screen existing patients, expediting the process tremendously. The light at the end of the tunnel is that there is a learning curve, and once an investigator can navigate through the most burdensome obstacles of a study, future research can be done in a more routine fashion.

Competition for studies is getting tougher. As more physicians look to replace the revenues lost from declines in reimbursement, interest in research is growing. Whereas experience is often a criterion for investigator selection, opportunities exist for first-time researchers as well. Because one of the most scarce resources of an effective study is an appropriate patient base, practicing physicians should not underestimate their ability to compete for studies. Additionally, investigators must market themselves. In doing so, their curriculum vitae should illustrate relevant credentials and certifications for clinical research.

Regardless of the perceived rewards, there are many challenges to entering into a clinical research study. To properly evaluate opportunities for research, clinicians must be prepared and knowledgeable of the demands they might face.

**SECTION III: OPPORTUNITIES FOR PHYSICIAN INVOLVEMENT**

CROs and drug sponsors generally look for two key qualifications in investigators—extensive patient base re-
want to the drug being tested and clinical research experience. Physicians interested in clinical research (having considered the issues discussed above) should look for ways to enhance their qualifications in these areas.

Before engaging in clinical research, physicians might want to participate first in Phase IV studies to evaluate their interest. Phase IV studies take place after a drug has been approved by the FDA, when the efficacy and safety of the drug can be tested in a larger population. For most Phase IV studies, physicians do not need to create a significant practice infrastructure.

Another opportunity for physicians is to work in conjunction with CROs or drug companies to develop or improve study design. A physician with extensive clinical knowledge of and experience with a particular disease or disorder can be very valuable in evaluating inclusion and exclusion criteria, creating clinical protocols, and designing report formats that increase the chances of yielding statistically significant results.

SECTION IV: INITIAL STEPS CLINICIANS CAN TAKE

Some initial steps physicians can take if they are interested in becoming involved in clinical trials include the following:

- Contact CROs and SMOs and ask for more information on future studies and investigator requirements. You may be asked some questions about your practice and patient base. Determine if they maintain a database of physicians.
- If you belong to a PPM, ask if it has considered helping physicians get involved in clinical research.
- Focus on established relationships. Ask drug representatives about possible research on a product (e.g., re-marketing opportunities, Phase IV studies). But be careful of drug sponsors’ hidden agendas.
- Talk to an experienced investigator and/or case coordinator about his/her experience. Maybe you can become a subinvestigator and learn the ropes.
- Review literature sources that assist clinicians in performing clinical research.

IN SUMMARY

The pharmaceutical industry and medical device industry, despite consolidation, are growing segments of the healthcare landscape. These companies look upon clinical practices as a source of clinical material to evaluate and bring their products to market.

Much of the consolidation we are seeing is largely motivated by a desire to increase productivity in R & D, putting more drugs and devices into the pipeline. However, these companies also confront the costly overhead structure and challenges of global reach, and also acknowledge what some perceive as an era of revolution in medical science as we revise and modify our traditional views of disease. The gross categorizations of disease processes such as hypertension, coronary artery disease, etc. may give way to new
nomenclature and classification as we delve into the molecular components of these pathologies. These new scientific and biological endeavors will form the basis of exciting new therapies that are only now beginning to enter the clinical sphere.

Some clinical practices are well positioned to partner with the industry and industry intermediaries such as CROs to assist in strategically collaborating to speed the development of therapies to market. These relationships are usually most productive when placed in the context of long-term time frames with appropriate practice infrastructure to support quality clinical research. Successful clinical practices will understand the importance of appropriate staffing and attention to detail in order to be looked upon as a valid business partner. Successful practices and practitioners in addition to bringing their patients and clinical acumen to the process do stand to benefit in garnering some new revenue streams, but it may not be the financial windfall some anticipate. Other benefits, however, may be as valuable. Some of these include:

- Prestige in your community and among your colleagues
- The ability to stay abreast of recent developments and new ideas in your areas of interest
- An opportunity to mingle with the thought leaders in a particular area of research

In addition, practices that have the appropriate infrastructure to support clinical research and commit to research on a long-term basis usually have the following characteristics:

- A better understanding of how drugs and devices move from the lab bench to patients
- An ability to set critical success factors for their performance in research
- Are helpful in eliminating failures and assist in the establishment of the next phase of testing
- Understand the nuances and precarious aspects of an effective drug or device launch
- Are good at rapid subject enrollment
- Implement strategies to augment and enhance a patient volunteer database
- Minimize down time in their research cycles
- Understand the benefits and take advantage of technological tools available to assist in rapid and reliable data capture and analysis
- Employ individuals who focus and manage the research components of their practices

The commitment to engage in clinical research is one that should not be taken lightly. Assuredly, if one does commit the appropriate resources and time, it is usually found to be a stimulating and rewarding undertaking - one that can pay dividends throughout one’s professional career.

“"The most reliable way to anticipate the future is by understanding the present.”"

—John Naisbitt
American Futurologist

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REFERENCES


14. The website www.clinicalinvestigators.com provides a list of CROs focusing on cardiology/cardiovascular disease.