

The Marketplace for Clinical Grants

The average costs of pharmaceutical research and development for a successful drug continue to increase, with costs frequently reported in excess of \$850 million from pre-clinical to FDA approval.¹ One of the largest single costs in that total is clinical grant spending, that is, those sums paid to sites and investigators to enroll and treat patients in accordance with clinical drug research protocols. The amount spent on clinical grants now exceeds \$7 billion a year worldwide and is continuing to increase.² As investigators conduct studies, with more procedures and more visits, the absolute cost per patient will increase. At the same time, more clinical studies and investigator sites also means more spending. However, once the study has been designed there are often major differences in the relative amounts paid to investigators doing comparable levels of clinical research. A number of factors explain these differences.

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Grant management is becoming ever more critical to a sponsor company's success. Likewise, grant spending is increasingly becoming an acknowledged market of buyers and sellers. Until the late 1990s, industry R&D professionals often preferred to minimize, and even avoid, the economic and business connotations associated with engaging clinical investigators to conduct clinical trials. Many still do. Even the somewhat anachronistic terms "investigator" and "clinical grant" hearken back to a less business-oriented environment. Grants are often associated with non-commercially related research. A few clinical investigators may seek funding from a pharmaceutical company to explore a specific topic related to a particular drug. Sometimes referred to by pharmaceutical companies as investigator initiated grants, these types of studies actually constitute a small percentage of funding spent to conduct clinical research. The vast majority of clinical grants represent a more standard type of contractual arrangement between the sponsoring pharmaceutical company and a clinical site to conduct research for the sponsor company. There can be extensive discussions between the parties about such research related issues as publication rights and additional research possibilities with the data. However, the final study data almost always belong to the sponsoring pharmaceutical company. Because of a long history of research usage, it may not be surprising then that the term "investigator grant" has remained in use. The term is certainly a more appealing one to many than clinical trial contract. (Clinical investigator is also more attractive than clinical research medical subcontractor.)

Undoubtedly, the clinical grant market has its own set of complications and unique characteristics. However, clinical grant spending is now more widely understood as a market similar in many respects to other business markets. It may be a market of scientific activity, but it is a business market nonetheless.

Since Nobel laureate Kenneth Arrow's seminal article on the health care market, an entire field of health economics has developed. Arrow highlighted some of the

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ways the market for health services differed from other economic markets.³ For many observers of the healthcare arena, the idea of a market-based system sits very uncomfortably with their concepts of a more equity-based healthcare delivery structure. For others, only a fundamentally market-based system offers the prospect of an efficient and cost-effective sustainable healthcare system. Whatever the role that people desire the market to play in overall healthcare delivery, clinical grant spending should more properly be viewed as a heavily market-based business arena. Supply and demand are important considerations in the business of clinical investigator recruitment.

Sponsor companies have begun to track and benchmark their own grant spending. However, sponsor companies have not all rushed to pay the same amount. On the one hand, some sites have requested higher amounts for a given level of work, while other sites have accepted lower levels. On the other hand, some companies have been willing to pay higher grant payments to specific sites on specific studies, while other companies have not. Market forces are at work. The data in Table 1 are illustrative. While the cost per patient paid in the United States has increased over time, the standard deviation has certainly not gotten smaller. The same pattern holds when we look at the cost per visit, or the cost per procedure, paid to U.S. investigators. There has not been a tendency for industry payment practices to con-

verge around a common figure or set of figures.

Comparative Spending Levels

Clinical studies are being conducted in more and more countries as pharmaceutical companies look for geographies where investigator sites are able to enroll and treat patients in a timely and cost effective manner. Grant levels paid to clinical investigators do vary appreciably by country for comparable levels of work.

The decision to conduct a clinical trial in a specific country is hardly ever driven solely by the comparative costs of conducting a study in that country. The local marketing company or drug development operation may indicate a strong interest in the particular medical need addressed by a specific clinical trial. The country marketing company may consequently be especially eager to participate in the clinical study and thus enlist the help of opinion leaders and other clinical investigator sites in that country's market.

The market potential for an indication may also be a critical variable in a company's decision to conduct a part of a multinational clinical trial in a particular country. Large pharmaceutical markets, even if expensive places for clinical research, will frequently need to be included in the study regardless of cost. Equally importantly, a country may possess particularly useful potential patient populations or medical expertise. As drug development costs soar, comparative costs are increasingly considered along with enrollment rates, medical expertise, and market potential as bases for deciding to include a specific country in a multinational clinical trial. As the clinical operations vice president at a major pharmaceutical company expressed it:

“Our major goal is to complete quality clinical trials in as short a time frame as possible. If we can

Table 1. Cost Per Patient Payment Practices in the United States

Year	Mean Cost Per Patient (\$)	Standard Deviation (\$)
1990	4,863	4,137
1995	5,691	4,343
2000	7,152	6,887
2003	8,116	7,212

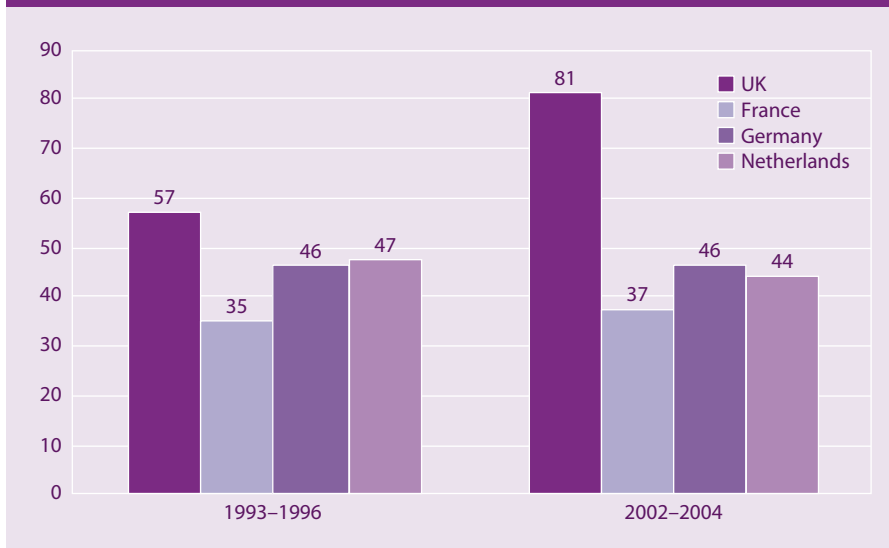
do that at a lower cost, we will. That often means conducting studies in areas where costs are one of the decision-making factors.”

Some countries are simply much more expensive than others as places to conduct clinical trials. Traditionally, the United States has been the most expensive country in which to conduct clinical trials, followed by the countries of Western Europe. In recent years many pharmaceutical companies have begun extensive clinical research activities in the less expensive areas of Eastern Europe and Latin America.

Figure 1 illustrates how much the relative costs of clinical grants for comparable levels of activity can vary by country, expressed in 2001 currency. The dollar has declined so substantially in the last couple of years that, in 2005 currency terms, many European countries approach American clinical grant levels when expressed in current dollars. Hence, the year 2001 was chosen to illustrate fundamental relationships between countries, particularly when examined over time. Compared to the United States, other countries may still be much less expensive in which to conduct clinical research, especially in Eastern/Central Europe and Latin America. The cost for a clinical site in the U.S. may be the equivalent cost for multiple sites in other geographies.

The reasons for the cost differentials are many and are often related to basic factors such as comparative living and medical costs. For instance, it is more

Figure 1. Comparative Phase II-III Costs Per Patient (US dollars) for Selected Countries As a Percentage of UK Costs (US=100 base)



expensive to live in London than in Bucharest. Some of the differences can also be tied to variations in clinical research practices. All clinical research, including outpatient indications, in Italy and Spain must be conducted through a hospital, which is traditionally a more expensive site than office-based practices. An example of changing clinical research practices can be found in England and Wales. In the last few years the National Health Service has indicated that hospital trusts in the United Kingdom must become more cost efficient. Of relevance to the pharmaceutical industry is the requirement that individual hospital trusts institute R&D committees, with the express goal of increasing clinical research revenues.

Figure 1 also demonstrates that the relative cost differences between countries may change over time. A case in point is the United Kingdom, which is becoming a relatively more expensive place to conduct clinical trials compared to other North American and European countries. Many would argue this increase is due to the overheads now charged by hospital trusts. For others it may also be a case of supply and demand. The UK remains a country

in high demand for clinical trials, while the number of sites to conduct clinical trials has remained relatively constant.⁴ UK clinical research grants were, on average, about half the cost of the United States in the mid 1990s for comparable levels of work, but increased to nearly three-quarters of the U.S. number by 2003. Strong demand for a limited number of sites, combined with specific National Health System strategies, have helped to push up UK costs faster than in many other countries.

Pricing practices may also differ across countries for budget areas, which may seem at first appearance to be similar. Institutional overhead rate is a case in point. Overhead in the United States varies by institution with the median overhead percentage of 24%, and a standard deviation of 5.6. The United Kingdom median figure is comparable at 25%, but the standard deviation of 11.3 is much larger.⁵ There is much more variation in UK institutional overhead rates than is the case in the U.S.

A Complex Market

A number of market dynamics are at work in understanding investigator grant

costs. Again, a good case is the United States. On the one hand, the demand for clinical sites has grown over the last ten years as has the availability of new sites, as indicated by the number of 1572s filed with the FDA. Certainly, some growth has come from sites outside the U.S. The sheer magnitude of the increase, though, is primarily related to increased clinical research activity levels in the U.S. For example in 1990, a total of 8,255 1572s were filed with the FDA, a number which mushroomed to 35,815 in 2000.⁶

Ultimately though, the cost per patient amount paid to a specific site is an interaction of the buyer and seller, that is, a function of the demand for and supply of acceptable investigator sites. The specific amount paid to a site is only too much if the buyer will not pay and only too little if the seller will not accept that amount.

The overall business relationship with investigators can be multi-faceted. For example, phase III investigators can be important potential customers for marketed new drugs. Most phase III investigators are practicing physicians and not necessarily internationally acknowledged opinion leaders. Yet these practicing physicians likely play an important role in influencing how other physicians prescribe the new drug. For over 50 years, the literature has pointed to the function that medical peers play in influencing how physicians prescribe drugs. Recent literature highlights the role that clinical trial investigators, in particular, have in influencing on a local level the patterns of practice of other physicians. "... physicians involved in clinical trials tend to be local opinion leaders who can influence local practice styles because their patterns of practice are adopted quickly by other physician-colleagues."⁷ These peer opinion leaders are practicing physicians whose opinions are valued by other practicing physicians.

A recent study by the University of the Sciences in Philadelphia (USP) compared the 18-month post-launch pre-

scribing behavior of two matched U.S. physician groups for 32 new outpatient drugs.⁸ One group of doctors participated as principal investigators in phase III clinical trials of these new drugs. Physicians in the second group were matched with the case physicians by a number of pre-study demographic and prescribing variables. These control physicians had not participated as principal investigators in any clinical trials for the previous five-year period.

For all therapeutic indications, investigator physicians made the study drug available to patients sooner, and more frequently, after product launch than did the control physicians, especially for first in class drugs. Investigators continued to prescribe more of the study drug during the entire 18-month period covered by the study. The incremental number of new prescriptions these physicians write is hardly vital to the new drug's success. However, the importance of clinical investigators extends far beyond the number of prescriptions they write. Clinical investigators may often act as local opinion leaders with their peers and serve as important conduits in the adoption of new prescription drugs to the many physicians who are not clinical investigators.

Ultimately, Phase III clinical investigators are selected for their ability to perform clinical research. However, investigators are also potential customers as well as influencers of customers. In few other major business decisions would contractors play as important a role in the marketing of a product or service as do clinical investigators, which complicates the grant payment negotiation process.

Investigator Expectations

Why do investigators participate in clinical trials? Based upon more than 100 qualitative interviews with investigators and other industry professionals, three general reasons seem fundamental: the investigators want to be smart,

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look smart, and generate incremental revenues.

Clinical investigators believe that by taking part in clinical trials they can gain access to new drugs for the investigator's specific clinical practice. Investigators are able to present potential new drug therapies to their existing and future patients. Reading about a new drug in a peer-reviewed journal is often useful, but is no substitute for seeing the drug work, or not work, with the investigator's specific patients. In addition, investigators are also able to talk with other physicians at investigator meetings about drug therapy challenges and possible responses. Many of the investigators also indicate that they enjoy the enhanced role that clinical trial participation allows them to play with practicing colleagues. Clinical investigators often feel that they are sources of new information for their colleagues about new drug developments. When a new drug comes on the market, investigators report that other doctors frequently ask questions about the investigators' clinical trial experience with the drug. According to one experienced clinical investigator:

"Sure I like going to investigator meetings in nice places. I like talking with other doctors about how they deal with similar issues. I also like that my colleagues back home ask me about the new drug when

sales reps call on them to talk about the new drug."

A third major reason for clinical trial participation is clinical grant money. Grants represent additional sources of revenues. In the U.S. the money may go directly to the physician or to the physician's practice. In some cases the grant money goes to the physician's hospital. In many cases the money is used for additional research activities of particular interest to the clinical investigator.

These qualitative results are consistent with an earlier quantitative study of American and European investigators. The study involved 193 clinical investigators in a full profile, conjoint trade-off analysis of their reasons for participating in a clinical trial.⁹ This kind of analysis is widely used to measure how important various factors may be in a decision to undertake a specific activity, in this case, clinical trial participation. Conjoint analysis enables us to determine mathematically the relative importance of various factors in the initial decision, as well as the trade-offs a person will make between those factors.

The physicians indicated that the relative grant price offered was an important consideration in their decision, particularly among young investigators. However, the therapeutic area of the study, the drug's therapeutic innovation, and the science associated with the study were critically important considerations as well. Physicians wanted to work in areas where they too could learn. For instance the data indicated that both American and European investigators would accept a substantially lower grant price in exchange for the opportunity to work with therapeutically novel drugs.

These investigators reported results in the conjoint study comparable to those from an empirical study of actual clinical grant payment levels for 2,108 phase III clinical investigators.¹⁰ Payment data in this study showed that investigators in the study accepted substantially lower

grant levels when they worked on a therapeutically novel new drug. The study looked at a range of variables influencing actual payment levels, including compound therapeutic novelty, protocol and study complexity, the investigator's clinical expertise in general, and clinical experience in the specific indication of the study drug, as well as clinical experience working for the particular sponsor company conducting the clinical trial.

Traditional economics teaches that markets exist when buyers and sellers interact. The interaction determines market prices and thereby allocates scarce goods and services. Prices send signals and provide incentives to buyers and sellers. When supply or demand changes, market prices adjust, which affects incentives. Competition among buyers increases prices and allocates goods and services to those people who are willing and able to pay the most for them.

The study provided empirical evidence that supply and demand for investigators is at work. The greater the market demand at any time for investigators, the greater the relative amounts they receive. In this study, as the number of studies being done at the same time in the same indication increased, the relative payment size also increased for investigators working in that indication. For each additional compound in Phase III clinical trials in the same indication as the study compound in this analysis, investigator payments increased 2.7 percentiles. As more studies are conducted in a given indication and the consequent demand for investigators increases, so does the relative amount paid to them by companies competing for investigators' services.

According to these data, experienced investigators also command a relatively higher price in the market. Likewise, as the number of clinical studies conducted by a specific investigator increased, so did the relative price commanded by that investigator.

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The study provided evidence that a combination of drug development and investigator and market dynamics drive grant payment levels.

Grant Payment Levels and Performance

The role of grant payments, and differential payment levels, has raised issues in the wider medical community. Some observers have challenged why some investigators are paid more than others for comparable levels of work, and question whether these differential payments are a method to influence subsequent prescribing of the study drug, potentially eroding the physician/patient relationship and the basic integrity of clinical research.¹¹ A recently published study by University of the Sciences in Philadelphia (USP) found that paying investigators relatively more than other investigators did not increase subsequent prescribing of the study drug. Nor did these payments increase prescribing of other drugs from the sponsor company.

The issue of clinical grant spending levels on study completion times is a question of growing significance, particularly as the amount spent on grants has escalated. Every time a study lags in the field, or top management makes a statement to the financial community about

the importance of a specific compound, the issue of grant spending levels surfaces somewhere in the respective drug development organization. Professionals in many companies can relate cases where increased grant spending has increased enrollment rates. Other professionals, sometimes in the same companies, have come to the opposite conclusion that increased spending levels have had little to no measurable affect on reduced study completion times. A previous study by the author determined that higher grant spending levels were not related to decreased study completion times.¹² However, if grant levels were very low, i.e., below the 25th percentile, study completion times appeared to slow. The relative grant level seemed to have little effect though on enrollment rates once the clinical agreements were signed, although lower payment levels did seem to lengthen the time it took to recruit sites. With low grant offers, a higher percentage of sites rejected the offers, with an increased amount of time required to complete the agreement. A number of variables explained why some studies finished faster in the field. These variables included such understandable study attributes as the indication, the study design, the complexity of the protocol, the patient treatment duration, and the number of patients enrolled.

If higher grant payments cannot be shown to improve study completion times in general, sponsor companies must understand if and when these payments do have the desired enhanced effect on project performance. Otherwise, money is being wasted. More importantly, the *opportunity* costs of the wasted money dwarf the value of the wasted expenditures themselves. Studies that could have been done to move products to market faster cannot be undertaken because of misspent grant spending.

Higher payments may be associated with faster performance at some sites and with some studies. Perhaps some

sites were more financially motivated than others. However, it may very well be that any positive result of higher payments is also associated with a type of Hawthorne effect. In a famous pre-World War II study at the Western Electric plant in Hawthorne Illinois, researchers found that improving working conditions enhanced plant performance. Oddly, as plant management modified, often substantially, the earlier changes, plant performance continued to improve. It seemed that the changes themselves were less important than the perception by the plant employees that management was devoting attention to them and their issues.

The same dynamic may sometimes be present with higher grant payments. High priority studies receive attention up to the highest levels in the corporation. High priority studies, especially if they are substantially behind schedule, may be the ones most likely to receive boosted grant spending levels. Important studies, of high management visibility, may be the ones receiving higher grant payments. This may be true for both initial agreements as well as any subsequent changes to those original agreements. The higher relative grant amount is less important than the study management attention in understanding faster completion times.

There is a potential paradox where proponents of higher payments and improved performance may sometimes be right and at the same time that advocates of the opposite position are also correct. For example, the relative grant amount may help explain performance at certain types of sites. Higher payments increase performance at some sites. However, the overall study performance may not improve because not all sites in the study are similarly motivated. Study completion time is ultimately slowed by the slowest enrolling site. Average, or selective faster enrollment, cannot overcome enrollment at the slowest site.

TTC and USP are currently conducting a comprehensive study with 10 major pharmaceutical companies to identify the

major factors explaining the role of clinical grant payments on individual site and study performance levels. The results will become available in 2005. TTC is a provider to the pharmaceutical industry of drug development data; USP has a long tradition in the pharmaceutical industry. Founded originally as the Philadelphia College of Pharmacy, USP counts many of the greatest names in industry history as graduates, members, teachers or trustees of the University, including such illustrative leaders such as Lilly, Wyeth, McNeil, Rorer, Wellcome, Burroughs, Kline, French, Warner, and Remington, to name but a few. As the results from this current research project become available, we look forward to sharing them with participants in the pharmaceutical and health care industries.

Conclusion

Pharmaceutical companies are increasingly adopting a model where a centralized grant negotiations group works with the individual countries and study teams to set project grant spending budgets. Dedicated grant negotiators are replacing CRAs as the contact with the sites for grant related issues. Leading edge companies are beginning to appreciate, and design grant strategies reflecting, that investigators will accept lower grant levels for the opportunity to participate in clinical trials of innovative compounds, for the prospect of continued work from the sponsor company, and for participation in better designed and executed studies. Throughout the entire process, sponsor company outsourcing management needs to appreciate the role that supply and demand ultimately play in grant agreements. Sponsor company negotiators must also appreciate the value that investigators have in the new drug adoption process. There is a delicate balance to be followed. Sponsor companies must pay a fair price at market rates, taking into account the importance of clinical investigators to new drug acceptance in the marketplace.

However, even within a specific geography, and for a given pharmaceutical company, grant payment differences may exist as market forces come into play with each grant negotiation between sponsor company and site. **ACRP**

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