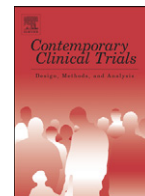




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Managing clinical grant costs

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ABSTRACT

The rapidly increasing cost of pharmaceutical R&D presents a major challenge for the industry. This paper examines one aspect of that spending, clinical grants, and presents ways that pharmaceutical companies can best manage those expenditures. The first part of the paper examines the role of clinical grant payments as a motivation for clinical trial participation. The second part outlines a number of current management practices for controlling clinical grant costs.

Financial compensation is an important matter for many physicians conducting clinical trials, especially those in office-based practices and those conducting phase 4 clinical trials. Since financial considerations are important to most types of investigators, and there is no compelling evidence that paying at high rates insures timely performance or quality data, companies engaging clinical investigators must manage their clinical grant funds as effectively as possible. Sound financial management requires that clinical development professionals appreciate the complex relationship between the pharmaceutical company and the physicians who serve as clinical investigators on that company's clinical trials. Sensible financial management of clinical grants also demands that sponsor companies get the most value for their clinical grant spending.

Ultimately, good clinical grant management requires an attitude that combines good business sense with an understanding that pharmaceutical R&D strives to bring to market new drugs that can help patient populations around the world. Investigators are medical contractors in clinical trials, and while they are engaged in their vital research, they are a part of the research process that must be carefully budgeted and managed. Society, pharmaceutical companies, clinical investigators, and patients will reap the benefits of adequately budgeted, and well managed clinical grants.

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Pharmaceutical executives report that the rapidly increasing cost of pharmaceutical R&D presents a major challenge for the industry [1]. The fully capitalized costs of a successful NDA are in the area of \$1 billion, with phase 2 and 3 clinical trials the most expensive area of direct expenditure [2]. This paper examines one aspect of that spending, clinical grants and presents ways that pharmaceutical companies can best manage those expenditures.

While we are learning about the full range of the motives prompting physicians to become clinical investigators, we do know that financial remuneration is an important consideration. Currently, the University of the Sciences in Philadelphia (USP), and TTC-Ilc are conducting a multi-year research program on the management factors affecting clinical trial completion. One of these factors is the management of the financial remuneration to the investigative sites. Our overall study examines, among other issues, the role that finances play in an investigator's decision to take part in a particular US clinical trial.

While other analyses have shown that the prospect of additional revenues is often not the most important

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motivational factor in an investigator's decision to take part in a specific clinical trial, financial considerations do play an important role [3]. The first part of the paper examines the role of clinical grant payments as a motivation for clinical trial participation.

The second part of the paper outlines a number of current management practices for controlling clinical grant costs. We argue that well-managed clinical research grant payment organizations have four traits in common. They are:

- Adequately staffed, and increasingly function as a dedicated, centralized component in the organization;
- Led by professionals who can communicate effectively and understand clinical research fully, as both a business and as medical activity;
- Operate with professionals who know the intricacies of clinical budgeting, country specific cost differences, and fair market value; and
- Appreciate effective negotiating practices.

We maintain that since there is no evidence that paying investigators more on a cost per patient basis increases a site or study's performance, a well-managed clinical research organization must manage clinical grant spending as effectively as possible, understanding and paying at market rates.

1. Background

1.1. Relative grant payment levels

The workload is usually the major element determining the absolute clinical grant amount paid to a site to take part in a clinical trial. The more complicated the study protocol and related flow sheet, the higher the absolute amounts paid to the participating clinical investigators. Studies that are more complex usually require more site time and resources [4]. However, there are frequently major differences in the relative levels of the clinical grants investigators receive for participating in comparable trials. These differences can even exist among investigators in the same trial, especially within the United States; some sites are simply paid more than others for the same level of work.

A number of factors may account for these differences, including where the clinical trial is located. Some cities, regions, or countries have higher costs than others do. Additionally, each investigator's specific site may have different overhead and costs structures. For example, office-based physicians often charge less than academic medical centers.

The nature of the compound may also influence grant levels. A case in point is a first-in-class compound. Studies show that some investigators are willing to accept lower grant levels to work on innovative new compounds. Yet even taking these cost factors into account, we find that some sites are more motivated to negotiate better deals. In the end, the dynamics of supply and demand are critical.

Market considerations can also heavily influence clinical grant levels. For instance, when many studies are competing for a fixed number of investigators, grant levels tend to rise. In addition, some sites with proven expertise, reputation, and negotiating tenacity will command premium prices in the investigator marketplace [5].

1.2. The investigator marketplace

The clinical grant market is a distinctive one. Forces of supply and demand are at work, but the relationship between buyer and seller is a complex one. Sponsor pharmaceutical companies and physicians participating in clinical trials have a two-way relationship because clinical investigators are: 1) both buyers and sellers of sponsor company products and 2) service agents, as they enroll and treat patients according to a clinical study's protocol design.

Additionally, clinical investigators can also play an important role after the study is completed and drug has come to market. Clinical investigators often prescribe higher amounts of a study drug from a clinical trial in which they took part, although no relationship exists between the relative grant amount paid to investigators and their subsequent prescribing of the study drug [6,7]. The incremental new drug prescribing level of these investigators is a tiny fraction of a new drug's overall prescribing volume. Yet, as practicing physicians, clinical investigators may recommend the trial drug to other practicing doctors [8–12]. Thus, investigators work as both a medical contractor and an important market influencer.

1.3. Grant payment levels and performance

Investigators of all types do consider financial remuneration in deciding whether to participate in a specific clinical study. However, no published evidence exists linking high sponsor per-patient grant payments to clinical investigators with improved study timelines or quality. Even among individual sites in a particular study, higher paid sites do not generally perform better than less highly paid sites. They do not enroll more patients more quickly, or deliver higher quality data [13].

2. Methodology

2.1. The sample

Using the Bioresearch Monitoring Information System File, we drew a random sample of 5000 US investigators, stratifying by number of 1572s on record for a specific investigator. Nearly 50% of the physicians in the FDA 1572 database have filed only one 1572. We under-sampled this large group, drawing only 25% of the sample from the one-time investigators. We were able to confirm the mailing addresses of 4355 physicians and sent a questionnaire to those investigators. According to our stratification design, 25% of questionnaires went to physicians with one 1572 on record with the FDA; the other 75% were mailed to investigators with more than one 1572 on file.

We sent two mailings to the physicians with valid addresses and re-mailed to investigators who did not respond to the first mailing. We received 762 useable questionnaires. This constituted a 10.6% response rate from the first mailing, and an additional response rate of 7% from the follow-up mailing, for a total response rate of 17.6% (Table 1).

While the average number of 1572s on record for each investigator is statistically insignificant between the original sample and the physicians returning a completed questionnaire (4.4 and 4.2 respectively), there is a slight difference in the response rate of completed questionnaires

Table 1

Survey return rates for 4355 sample and the 762 completed questionnaires

Number of 1572s	Total study sample (%)	Completed questionnaires (%)
1	25	23
2 or more	75	77
Mean 1572s	4.4	4.2

by the two strata. A somewhat slightly lower percentage of investigators with one 1572 returned questionnaires, while a slightly higher percentage of investigators with more than two 1572s returned a completed questionnaire.

2.2. The questionnaire

During the construction of the data collection questionnaire, we conducted a series of interviews with clinical investigators and drug development professionals. We pre-tested the questionnaire with several experienced clinical investigators and incorporated their suggestions into the final document. A copy of the complete questionnaire is available at the study Web site, which also provides the total set of respondent answers to the questionnaire questions [14,15].

The questionnaire incorporates a list of twelve reasons why an investigator might participate in a specific clinical trial. We asked respondents – on a scale of 1–10, with 10 being very important, and 1 not important at all – how significant each of the twelve reasons would be for their participation in a phase 3 clinical trial of a new compound being tested by a pharmaceutical company. To eliminate potential response bias due to the order of the questions, we systematically rotated these individual items in five versions of the questionnaire. For our analysis, we considered any response between 8 and 10 as important.

Additionally, we obtained detailed information on the nature of the physician's practice, prescribing levels, demographics, and research experience. IMS Health supplied the physician prescribing data as well as supplementary information on the physician demographic data.

3. Findings: financial considerations and clinical trial participation

Physicians in our study indicated a number of individual reasons for taking part in a clinical trial. Through factor analysis, we can summarize the individual reasons in three categories: 1) the chance to contribute to medical innovation;

2) specific aspects of the study and the organization running the study; and 3) financial considerations. Most of the physicians in this study considered medical innovation to be of paramount importance in their joining a clinical trial. They also cited opportunity to work on innovative new drugs, especially if these new compounds presented new therapeutic options for their patients. In the area of medical innovation, investigators welcomed the opportunity to interact with other physicians taking part in the clinical trial, and the chance to share their clinical research experiences using the study compound with other practicing physicians who may or may not take part in a clinical trial. For a more detailed presentation on these findings and a discussion of the methodology, see [3]. Investigators were also attuned to other issues, including the reputation of the company sponsoring the study, whether a CRO or sponsor company was running the project and their experience with the organization running the study.

Still, the prospect of receiving clinical trial revenues can be an important motive for many clinical investigators. Forty-three (43) percent of the investigators indicated that these incremental revenues were very important to their practice, institution or department, and prompted them to participate in a particular clinical trial. For the other investigators (57%) indicating that incremental revenues were not an important consideration, these revenues may still have played some role in their decision-making.

The clinical research experience is similar for the two types of investigators, those for whom financial considerations are very important and those investigators for whom these considerations are not. The two sets of investigators report similar level of phase 2 and 3 clinical experience over the last three years, and have a comparable number of 1572s on file with the FDA. Both groups have also done a majority of their work in trials managed by CROs. The two groups do differ somewhat though in their phase 4 experience. More financially attuned doctors have, on average, done more phase 4 clinical trials than the physicians who did not consider remuneration to be a major factor in their decision to join a clinical trial (Table 2).

With one important exception, type of practice, there is little difference in the demographics and practice characteristics between those for whom financial considerations are very important, and those for whom it is not. Doctors who placed greater importance on remuneration did not differ in any significant way from the other investigators by age, gender, level of involvement in direct patient care, type of

Table 2

The importance of additional revenues as a reason for participation in clinical trials and an investigator's research experience

	Number of phase 2 clinical trials as a principal investigator over the past three (3) years	Number of phase 3 clinical trials as a principal investigator over the past three (3) years	Number of phase 4 clinical trials as a principal investigator over the past three (3) years *	Percentage of the investigators clinical trials managed by CROs over the last three (3) years	Number of 1572s on file with the FDA 2002–2005
Investigators for whom revenues are very important	5	11	5.2	64%	6.1
Investigators for whom revenues are not very important	4.6	10.8	2.2	61%	5.6

ANOVA *P=.05. SPSS version 15.

specialty, or the percentage of time they spent at their primary and secondary hospital. Nor was there a difference in the overall volume of prescriptions both groups wrote.

A majority of clinical investigators in the United States are office-based [16], which held true for investigators completing study questionnaires. Statistically, the prospect of additional revenues is significantly more important to office-based physicians when we compared their answers to the study questionnaires with investigators who work in hospitals, medical schools, teaching hospitals, research centers and other types of practices. Half of the office-based physicians indicated that incremental income was a very important consideration in their decision to take part in a clinical trial. The numbers are less for other investigators in other types of practice settings, dropping to 25% for hospital-based investigators (Table 3).

4. Discussion

Financial compensation is an important matter for many physicians conducting clinical trials, especially those in office-based practices and those conducting phase 4 clinical trials. Since financial considerations are important to most types of investigators, and there is no compelling evidence that paying at high rates insures timely performance or quality data, companies engaging clinical investigators must manage their clinical grant funds as effectively as possible. Companies can take a number of steps to improve the effectiveness of clinical grant management.

4.1. A dedicated central grant management function

In recent years, the pharmaceutical industry has come to better understand the complex relationship between a pharmaceutical company, its agents (e.g. a CRO), and clinical investigators. This understanding, coupled with the large sums expended on clinical trial agreements, has led pharmaceutical R&D organizations to look for ways to maximize the value of their clinical grant spending. For example, the industry has moved closer toward some form of a fully staffed centralized grant management function, as distinct from the financial function. This activity was traditionally located in various parts of the R&D organization, such as finance, purchasing, clinical operations, and the therapeutic areas. However, the predominant pattern in many companies today is to locate the function somewhere in, or close to clinical operations, often as part of a central clinical outsourcing unit. Increasingly, the industry views grant management and investigator negotiations as requiring a detailed understanding

Table 3

Percent of investigators for whom supplemental income is an important reason for participating in clinical trials by type of practice

Office based*	Academic medical center/other teaching or research center	Hospital or hospital affiliate based	Other (e.g. administrators, or surgicenters)	Total
%	%	%	%	
50	38	25	43	
n 365	300	63	21	749

*Chi Square $P=.05$, SPSS version 15.

of protocol design, finances, and clinical operations. Companies view a dedicated function as being able to create and apply necessary standards and processes, which may require such seemingly simple steps as common report formats. According to one clinical development vice president:

“If you don't have the operating units reporting their activities and grant costs in a common format you simply cannot make informed judgment. We have found that a dedicated function can do this better.”

Senior R&D management looks toward the centralized function to provide stronger financial oversight of clinical grants, starting with the annual budgeting process. According to one executive:

“Clinical grants represent a great amount of money. It has to be managed like any other area. We need to get a good return for our expenditures. We look to a central function to measure and track performance against the goals. They have to co-ordinate with the project teams and countries. But the whole area needs central oversight.”

Because pharmaceutical companies need to insure that they receive effective value for the funds they spend on clinical trial agreements, there has been a growing sense that they should handle their annual clinical grant budgeting process through a central function. This viewpoint considers the funds a pharmaceutical company spends on clinical trial agreements to be a senior management decision.

The centralized function handles the grant budgeting process. Working with the project teams and the appropriate field clinical operations units, the centralized function assembles the grant budget for the individual projects and tracks performance against overall and project budgets. However, for a central grant management operation to be most effective, senior drug development management must recognize that substantial levels of effort are required. Many senior drug development leaders believe that the management of such large sums increasingly justifies allocating more staffing and resources to this function.

4.2. Grant management skills and knowledge

The successful planning, budgeting and negotiation of clinical grants requires incumbents with a variety of skills and knowledge bases. In addition to communications and financial skills, success in this area requires individuals who have a full understanding of how drugs are developed. To understand the content of clinical trial agreements, grant management needs a solid grounding in the structure and processes of clinical trial design and implementation. To be accepted by the other key company actors affected by clinical grants, including the study teams, country clinical operations and the therapeutic areas, grant managers must have effective internal and external communications skills.

Moreover, effective grant spending requires that grant managers know the market rates for clinical grants. In recent years, pharmaceutical payments to physicians have received public attention; this is certainly true for grant payments. To avoid any perception of a conflict of interest, the grant managers

from the sponsor company should know fair market rates for clinical research, and should understand how important it is to pay those rates to physicians conducting clinical research [17].

4.3. Effective budgeting

Effective grant budgeting begins as soon as a protocol is conceptualized with a general idea about procedures and office visit schedules. Companies can improve their budgeting by appreciating common practices that may lead to over-budgeted studies. For instance, they must know the actual market rates for a study, particularly for all the countries involved in that study. A critical error is to assume that the grant payment levels for the most expensive country in a multi-national study must be paid to all the sites in that study, regardless of the market rate specific to that country. Companies can improve their budget assumptions by understanding the early feasibility work, by knowing market rates over time, and by discussing rates with individual country clinical operations personnel and informed professionals.

Too often a company may think only in terms of total cost per patient and completed patients. Effective clinical grant budgeting is not merely putting costs to the fully loaded activities involved in a completed patient's participation in a clinical trial. Inaccurate screening and poor assumptions about drop out rates can dramatically affect budgeting assumptions and the actual cost per patient paid to investigators. Companies can avoid these problems through better initial planning and regular budget updates that provide up-to-date information on actual drop out rates. As part of the budgeting process the grant management team must be able to understand and, if necessary, challenge the screening failure and drop out assumptions used by the clinical team.

The use of cost per visit financial agreements with the sites provides more financial flexibility to the sponsor pharmaceutical company. For instance cost per visit agreements allow the sponsor company to pay more easily for partially completed patients who have dropped out of the study. With the use of cost per visit agreement, there is less need to negotiate with the sites about which part of the total cost per patient should be paid for these patient drop-outs.

Over-funding and under-funding can both present problems for companies. Clinical studies may run behind their originally budgeted and planned schedule so that actual payouts fall short of the total amounts put in the budget for clinical grants. Under-budgeted projects can also force project teams to request additional funding.

Over-budgeted projects can be even more damaging. Budgeted money is frequently spent money. In most organizations, once money has been budgeted few people are eager to go back and revisit the budget, unless they feel that amounts budgeted are inadequate for the task. Over budgeting of clinical grants can lead to wasteful spending. However, just as important, over-budgeted projects can represent additional opportunity costs: money required for other projects is wastefully spent or remains blocked for long periods on studies that will never use the funds. As one R&D executive interviewed for this research indicated:

“We can't manage well if we have large budgeted grant sums that we do not spend. We need to have access to those funds for other important studies.”

The grant management group should also be prepared to tell the study team and therapeutic areas how the protocol design is affecting study costs. Ultimately, the protocol design must reflect the company's long-term medical and marketing needs. However, the medical activities in many protocols may be overly complex and costly, leading to unnecessary costs that the design team may simply not have appreciated. A simple reference back to the study team can eliminate major study costs. Such an exchange may cut non-critical procedures and activities and reduce redundancy. At first, the costs of an individual procedure may appear substantial. However, when that procedure is conducted multiple times with many patients, the financial impact may be far more substantial than was anticipated in the study design phase. This is particularly true for oncology studies, where one must be clear to indicate when to perform a procedure and not simply rely upon standard of care information when it becomes available.

Wherever possible, budgeters should incorporate standard of care assumptions into all budgets and site agreements. Costs related to standard of care do not necessarily need to be paid for again in the grant agreement, as the investigator may be reimbursed for that procedure from other sources.

Ultimately, there is no substitute for a good understanding of the cost components of a clinical budget. There are traditionally three financial parts to a study specific protocol: the flow sheet of medical procedures; the other direct, non-flow sheet, costs such as wages and salaries and pharmacy; and overhead, if relevant. To create an effective study budget, companies need solid information for the flow sheet. They must know other direct costs and overhead, add the appropriate funds for screening failures, and subtract the appropriate funds for drop-outs. For example, in estimating site staff costs, companies must understand the time actually used by a staff member and then combine that information with up-to-date salary data for those involved in conducting the study and for administration.

Throughout the process, effective grant managers work closely with the individual country operations involved in a particular clinical trial. Often, it is valuable to explain to the individual countries and even to the investigators themselves, the reasoning behind the financial levels in the cost per patient figure and the individual parts that go into constructing the cost per patient amount. According to one experienced grant manager:

“The project team and investigators may not always agree with you. But the chances improve a lot if they understand how you came up with the budget numbers that you did.”

5. Conclusion

As spending on R&D and, in particular, clinical development increases at substantial rates, managing clinical trial agreements continues to increase in importance. While investigators cite a number of reasons for participating in clinical trials, almost all investigators report that financial considerations are a very important issue. Yet there is no evidence that paying at higher cost per patient levels improves site or study performance. This drives the need and fiduciary responsibility for effective cost management.

Sound financial management requires that clinical development professionals appreciate the complex relationship between the pharmaceutical company and the physicians who serve as clinical investigators on that company's clinical trials. Sponsor pharmaceutical companies must manage their financial relationship with sites in ways that ensure that they appear to, and actually do, pay fair market rates.

Sensible financial management of clinical grants also demands that sponsor companies get the most value for their clinical grant spending. Central clinical development – including grant management, the study teams, and the therapeutic areas – must work closely with each other and the country-level clinical operations personnel to ensure that they spend no more than the market requires to secure the agreement of the investigators the company wants to conduct its studies.

Higher than necessary payments to investigators do not improve performance. An appropriate organizational structure and management processes improve the chances of good clinical grant management. Spending should reflect company and site needs, along with market realities. Ultimately, good clinical grant management requires an attitude that combines good business sense with an understanding that pharmaceutical R&D strives to bring to market new drugs that can help patient populations around the world. Investigators are medical contractors in clinical trials, and while they are engaged in their vital research, they are a part of the research process that must be carefully budgeted and managed. Society, pharmaceutical companies, clinical investigators, and patients will reap the benefits of adequately budgeted, and well-managed clinical grants.

References

- [1] Glass H, Poli L. Connecting the dots. *Pharm Exec* January 2007:56–8.
- [2] DiMasi JA. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003;22(2):151–85.
- [3] Glass H. The importance of medical innovation in an investigator's decision to take part in clinical trials. *Drug Info J* 2008;42:537–43.
- [4] Glass H. Higher payments to investigators don't speed study completion. *Appl Clin Trials* 1995;4(11).
- [5] Glass H. Do clinical grant payment practices in phase 3 clinical trials influence subsequent clinical investigator prescribing behavior? *Disease Manage* 2004;7(1):77–87.
- [6] Corrigan M, Glass H. Physician participation in clinical studies and subsequent prescribing of new drugs. *Pharm Ther* 2005;30(1):60–6.
- [7] Glass H, Dalton D. Profiles of phase IV investigators and subsequent prescribing of the study drug. *J Pharm Mark Manage* 2006;17(3/4):3–17.
- [8] Guldal D, Semin S. The influences of drug companies' advertising programs on physicians. *Int J Health Serv* 2000;3:585–95.
- [9] Soumerai SB, McLaughlin TJ, Gurwitz JH, et al. Effect of local medical opinion leaders on quality of care for acute myocardial infarction: a randomized controlled trial. *JAMA* 1998;279:1358–63.
- [10] Soumerai SB, Majumdar SR, Lipton HL. Evaluating and improving physician prescribing. In: Strom B, editor. *Pharmacoepidemiology*. 3rd ed. Toronto, Canada: John Wiley & Sons; 2000. p. 483–503.
- [11] Greer AL. The state of art versus the state of science: the diffusion of new medical technologies into practice. *Int J Technol Assess Health Care* 1988;4:5–26.
- [12] Naylor CD. Better care and better outcomes: the continuing challenge. *JAMA* 1998;279:1392–4.
- [13] H. Glass and J. DiFrancesco, Understanding site performance differences in multinational phase III clinical trials. *Int J Pharm Med* 21;(4): 279–286.
- [14] University of the Sciences in Philadelphia and TTC's Investigator Site Survey: http://www.ttc-llc.com/Surveys/Profiles_of_Clinical_Invs_Questionnaire.pdf. July 2007.
- [15] University of the Sciences in Philadelphia and TTC's Investigator Site Survey Result: http://www.ttc-llc.com/Surveys/Profiles_of_Clinical_Invs_Results.pdf. July 2007.
- [16] Glass H, Beaudry D. The demographic, practice, and prescribing characteristics of US clinical investigators. *Drug Info J* 2007;41:645–51.
- [17] Glass H. Clinical grants under the microscope: what is a fair market value? *Good Clin Pract J* August 2006:23–5.

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