

# Why Investigators Take Part in Clinical Trials

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**S**tepped up investment in pharmaceutical R&D means many more studies, more subjects, and more sites. And that means growing demand for effective clinical investigators. The nearly threefold increase in the number of 1572 forms filed with the FDA between 1991 and 1998 illustrates the growing demand for study sites. In the face of increasing competition for investigators, sponsor companies may benefit by considering the factors that motivate an investigator to become involved with a particular trial.

The traditional clinical investigator model—particularly in Europe—explains investigator participation in trials by coupling the value of scientific innovation with direct improvements in patient care. That model treats financial considerations as almost insignificant. Although those assumptions may be true for some investigators, it seems unlikely that the model captures the dynamic currently at work in the U.S. and European investigator markets. For some investigators and institutions today, clinical research programs represent important additional revenue sources. Indeed, the consumer media have pointed to financial rewards for investigators and sites as an increasingly common factor in decisions to participate.<sup>1,2</sup> According to recent articles, the growing volume of clinical research and the increased sums paid to investigators for each subject treated are combining to make clinical research more attractive to physicians. Investigators, as individuals or as part of a practice, may negotiate directly with the sponsor company for additional compensation. At the same time, many institutions face growing pressure from internal cost control programs, capitated patient reim-

bursement from third parties, and cutbacks in government support, which means they are looking for new sources of revenue. Clinical research can help to fill bed capacity and bring in outpatient revenue.

To gain an understanding of prevailing investigator motivation and how a resourceful sponsor company can better leverage this knowledge, we surveyed investigators in the United States, the United Kingdom, the Netherlands, and Germany. Their responses indicate that the reasons that investigators in the United States and

Europe participate in clinical studies are more alike than many might anticipate. And their motives are growing even closer.

**The respondents.** As with any voluntary survey, there can be sampling biases. For instance, one might make the argument that the respondents in this study were more commercially oriented than those who did not respond because they took the time to complete the questionnaire. Conversely, one might assert that a commercially oriented investigator would not have taken time to participate in a study with no direct financial or other obvious commercial advantage to the

respondent. Thus, no claim is made that the sample is random. We maintain a listing of experienced clinical investigators; we sampled a range of these investigators by such key categories as country, nature of practice, number of clinical studies conducted at the site, and percentage of the site's studies conducted with CROs.

Of the 1848 investigators contacted by fax, e-mail, or mail, 193 investigators—or 10%—returned valid questionnaires. The number of respondents from the United

**A survey of investigators can offer sponsors some helpful ideas for recruiting investigators in today's increasingly competitive environment.**

**TABLE 1 Investigators and Phase 3 sites**

Investigators	U.S.	European
Mean number of clinical trials conducted at site <sup>a</sup>	19	14
Investigator's mean years of experience conducting clinical trials <sup>b</sup>	12	13
Investigators in practice providing direct patient care	68%	30%
Investigators at institutions (hospitals, schools, research clinics)	32%	70%
<b>Sites of Phase 3 trials since 1997</b>		
Private practice	63%	35%
Institutions such as hospitals, medical schools, and research clinics	37%	65%

<sup>a</sup>The number of trials ranged from 1 to 150 for U.S. investigators, 1 to 250 for Europeans.

<sup>b</sup>Experience ranged from 0 to 28 years.

States was 74; from the United Kingdom, 57; the Netherlands, 42; and Germany, 20. Table 1 shows brief breakdowns of respondent demographics and the types of sites where their Phase 3 trials have taken place since 1997.

On average, U.S. sites in the survey have conducted a few more studies; but the average clinical research experience of U.S. and European respondents was very similar. U.S. and European investigators do differ as to site location; 68% of U.S. investigators reported working in general and specialist practices, whereas 70% of European investigators stated they are in institutional settings. This split by practice type closely mirrors the actual breakdown for clinical research sites in the United States and Europe—which is contained in a proprietary database to which most major pharmaceutical companies have contributed confidential data on their active clinical grant costs.<sup>3</sup> The database thus represents a near census of current industry clinical grant activity. Grant information in the database is coded to indicate whether the site is an institution, hospital, or some other type of site such as private practice.

### Conjoint trade-off analysis

We conducted a full-profile conjoint trade-off analysis of the survey data. 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 trials participation. People rarely make decisions based upon one element at a time, but reach decisions after considering a number of intertwined elements—usually considered at about the same time. And, this kind of analysis provides a way to mathematically describe the trade-offs people make when weighing the factors involved in their decisions.<sup>4,5</sup> Thus, conjoint analysis helps us toward understanding the variables and the trade-offs that investigators consider when deciding whether to participate in a clinical trial. It can also show us how U.S. and European investigators compare.

The investigators' decisions can have direct consequences for sponsor companies. Based upon their trade-offs, for instance, can a sponsor reasonably expect that the investigators will accept lower grant prices for clinical trials involving innovative new drugs? If so, how much less will be acceptable? Similarly, will an investigator accept smaller grants from a company with a

reputation for writing good protocols and case report forms (CRFs)?

Based upon a series of preliminary interviews with sponsor companies and clinical investigators, we developed and pretested a six-variable conjoint design (see Variables box). We presented the investigators with a number of carefully constructed clinical trial scenarios, and asked them to rate—on a scale from 0 to 100, with 0 being not at all likely and 100 being extremely probable—the likelihood that they would participate in the clinical trial described in each scenario. Each clinical trial scenario covered the same six-variable set, but the considerations under each variable were randomly rotated across the clinical trial scenarios. The study's orthogonal design—which means that there is no correlation between any of the variables—enabled us to measure investigator preferences and trade-offs more accurately.

### Deciding to participate

The importance scores graphed in Figure 1 summarize the relative importance to U.S. and European investigators of each factor they consider when deciding whether to participate in a clinical trial. (Complete models for U.S. and European respondents to the survey are shown in Table 3.) Except for the scores for sponsor versus CRO monitors, importance scores in the two models are statistically significant at the 0.001 level or better—meaning that the chances of obtaining these particular results are less than 1 in 1000.

The importance scores are in standard units, or beta values, in which a factor with a score of 30 is twice as important as one with a score of 15. These standard units are mathematically comparable across variables. Because the six variables in the design are orthogonal, and thus, not correlated, we can explore the trade-offs that investigators are likely to make between the variables by looking at the relative size of the standard units, or beta scores.

**U.S. and European investigators compared.** The general similarity between the European and U.S. data is noteworthy because of the relative importance each investigator group places on the

## Variables in Analysis

Investigators were asked to rate how likely they would be to participate in a given trial. The survey was designed to assess the relative weight of the following six variables.

**The sponsor company's reputation for writing good protocols and CRFs.**

The sponsor's reputation was either average or strong.

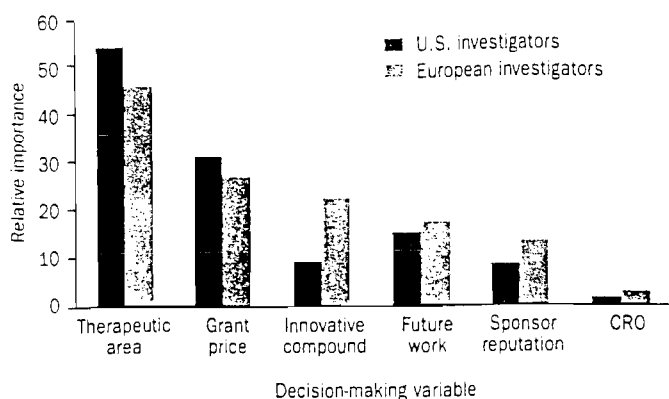
**Opportunities for future work.** There was either little or significant likelihood of obtaining future work from the sponsor company.

**Whether the compound was innovative.** The compound was described as either innovative or not innovative.

**Therapeutic area of expertise.** The study was either in the investigator's own therapeutic area of expertise or in another area.

**Site monitoring.** Site monitoring was handled either by the sponsor company or by a CRO.

**Final grant price.** Prices were 25% less, equal, or 25% more than what the investigator would normally accept for a comparable study.



**Figure 1.** The relative importance of factors investigators consider when deciding whether to participate in a clinical study. Therapeutic area of the study ranked first among respondents, and financial reward was second.

variables used in the full-profile conjoint model. Both groups indicate that the most important factor influencing their willingness to take part in a specific clinical trial is whether the study is in the investigator's therapeutic area of expertise. The data clearly indicates that financial considerations significantly affect participation for both groups. The size of the expected grant ranked as their second most important consideration, although Europeans place slightly less importance on final grant price in their decision making. Europeans place more importance on the product's level of innovation than do the U.S. respondents, a bit more importance on the prospect of future work with the sponsor, and somewhat more importance on the sponsor's reputation. Whether a CRO or sponsor company does the monitoring is of little consequence to investigators on either side of the Atlantic.

### Price elasticity and trade-off

In addition to allowing comparisons between variables, the conjoint model provides an opportunity to look at price elasticity—the degree to which a person is sensitive to differences in prices—for a range of grant prices. Prices in the model ranged from 25% less than the amount the investigator would normally accept for a comparable study to 25% more than the investigator normally receives. As Figure 2 shows, all other things being held equal, investigators in both Europe and the United States would rather be paid more for a given unit of work than less. Had the results been otherwise, we would have been forced to question the validity of our model or the participants' understanding of the exercise.

The severe slopes on the graph also reflect the similar price elasticity reported by both groups. Both European and U.S. investigators place the greatest positive value, as shown in standard units (beta scores), on the highest grant price in the model—that is, 25% more than what they would usually have accepted for a comparable study. U.S. investigators are more sensitive to the initial drop in price as it approaches their customarily expected level. But the initial divergence between U.S. and European investigators disappears at the lowest price level in the model—in this model, 25% less than the investigators would normally expect to receive for a study.

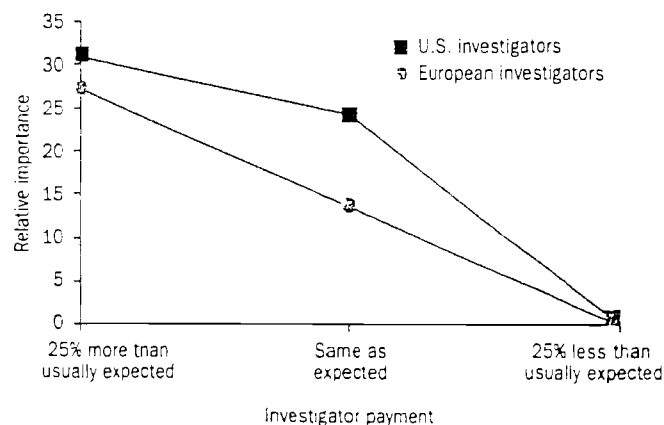
### Speeding study completion

Completing quality studies in a timely fashion is of paramount importance to pharmaceutical sponsor companies. But as a previous study demonstrated, paying more to investigators does not ensure faster study completion.<sup>3</sup> Yet, pharmaceutical R&D costs continue to escalate and R&D senior managers require that their employees manage costs as effectively as possible. Understanding the grant price trade-off investigators will make in relationship to other key study factors can provide insight into ways to better manage grant costs in the United States and Europe.

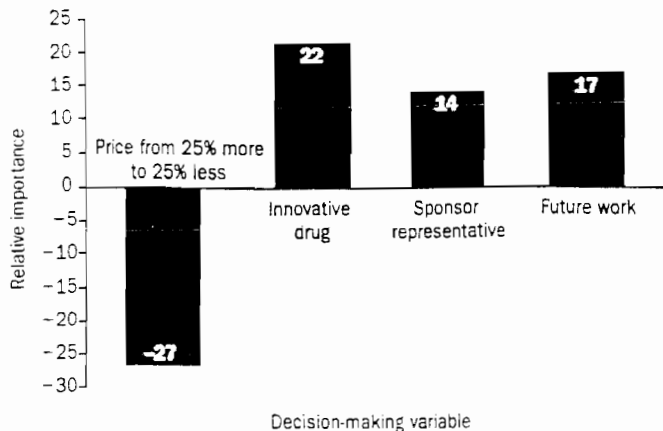
Many managers of clinical research programs are already aware that investigators may be willing to work for smaller per-subject amounts when given the chance to participate in a clinical trial involving a novel drug. Responses to our survey confirm this widely held notion and add credibility to the model—in which 10 standard units of value for one variable are equivalent to 10 units for another. Figure 3 shows how the trade-off model works.

Using the European data, for example, we see that European investigators associate a negative 27 units with a decrease in grant from 25% more than what they would usually expect to receive for a study to 25% less. In contrast, these investigators demonstrate a positive 22 points for working in a study with an innovative drug. In principle, then, investigators in our study would be willing to trade off a substantial reduction in grant price to work on such a study, according to our model. Trading off the positive 22 favorable units that European investigators place on a novel compound against the negative 27 units for the lowest price suggests that investigators would be willing to trade off a lower grant price for other factors—such as the prospect of working with a company adept at protocol and CRF design, or one that affords a likely prospect of future work. Other such factors could easily offset the 5 negative units not offset by the novel compound.

A real-world example can help illuminate the impact of price trade-off. According to the database referenced earlier, the average western European cost-per-subject for a 12- to 20-week Phase 3 outpatient study in hypertension is currently about



**Figure 2.** Price elasticity in decisions about trial participation—that is, the degree to which investigators are sensitive to payment prices. Respondents made it clear that their interest in a study diminished if they were offered a grant lower than their customary price.



**Figure 3.** Trade-offs between price and other considerations for European investigators. Investigators may be willing to work for less money if the study involves an innovative drug.

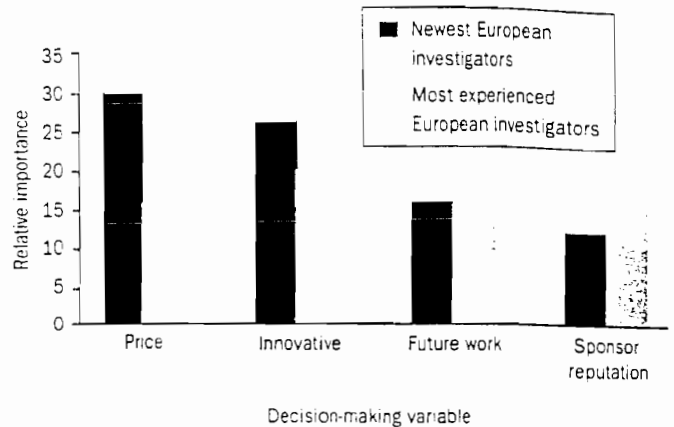
\$2200. For a comparable study with an innovative hypertensive product, an investigator would be willing, on average, to accept a grant price of about \$1800 ( $22 \div 27 \times 100 = 81\%$ ; 81% of \$2200 is \$1800). Similar trade-offs can be calculated for the other individual decision-making considerations in the model, or for combinations of those variables.

**Leveraging quality design.** Although clinical operations rarely have much control over the number of innovative drugs they can bring to field studies, they can leverage their market reputations and improve the quality of their CRFs and protocols. Furthermore, superior CRFs and protocols are likely to also have a positive effect on the timeliness and quality of a study's completion. And, our data suggests, those documents can also affect the per-subject grant costs that investigators will accept. The European investigators in our survey put a 13-point positive valuation on the ability to work with a company with a reputation for good protocols and CRFs—and are therefore likely to trade off price to work with such a company. Thus, well-designed protocols and CRFs can save time and improve quality. A resourceful sponsor company can also use those factors to reduce grant costs. Similarly, the positive values that investigators place on the prospect of future work should enable large sponsor companies, or sponsors with a dominant position in a therapeutic area, to pay a lower rate to investigators.

### The changing European investigator

An important generational change may be taking place among European investigators, with final grant price becoming more important. Responses to this survey are all from 1999, so we cannot assess a trend over time. Nevertheless, we can draw inferences from the differences in responses by investigator experience, as indicated by the number of years the investigator has been conducting clinical trials. Newer European investigators—those with 5 or fewer years of experience—tend to put distinctly more emphasis on price than do their most experienced counterparts—investigators with 15 or more years of experience conducting clinical trials.

Trends also emerge from other variables. Figure 4 compares reported importance of four factors for new and experienced European investigators. Both subsets report that the study's



**Figure 4.** The survey results suggest that newer European investigators are more motivated by financial concerns than their more experienced counterparts. The difference in the price variable is statistically significant at the 0.05 level.

therapeutic area is critical, and that who does the monitoring is of least importance. The most experienced European investigators, however, put final grant price behind compound innovation and the prospect for future work from the sponsor company. The

**TABLE 2 Study data: A conjoint analysis<sup>a</sup>**

U.S. data					
Variable <sup>b</sup>	B	SE B	Beta	T	Sig T
Therapeutic area	-39.140	1.625	0.544	-24.082	0.0000
Sponsor reputation	-5.444	1.625	0.075	-3.350	0.0008
Price 1	17.131	1.990	-0.238	8.606	0.0000
Price 2	25.638	2.298	-0.308	11.154	0.0000
Compound innovation	-6.464	1.625	0.089	-3.977	0.0001
Site monitoring	-1.021	1.625	0.014	-0.629	0.5296
Future work	-10.775	1.625	0.149	-6.630	0.0000
(Constant)	66.710	2.437		27.363	0.0000
European data					
Variable	B	SE B	Beta	T	Sig T
Therapeutic area	-30.743	1.235	0.458	-24.874	0.0000
Sponsor reputation	-8.716	1.235	0.130	-7.052	0.0000
Price 1	8.933	1.513	-0.133	5.902	0.0000
Price 2	21.073	1.747	-0.272	12.056	0.0000
Compound innovation	-14.880	1.235	0.222	-12.039	0.0000
Site monitoring	-1.794	1.235	0.026	-1.452	0.1468
Future work	-11.067	1.235	0.165	-8.954	0.0000
(Constant)	71.464	1.853		38.547	0.0000

<sup>a</sup>The conjoint importance scores in Figure 1 derive from the beta scores in Table 2; for example, U.S. investigators place an importance of 0.544 on therapeutic areas compared to a European score of 0.458.

<sup>b</sup>For those interested in more detailed analysis, B represents the unstandardized coefficient of the raw data, from which is derived SE B (the standard error of B); the beta score, which uses a Z score to make the coefficients more comparable; and the T score, which is the coefficient divided by its standard error. Sig T shows the significance of the results—that is, the chance that the data would have resulted from chance alone.

newest investigators put distinctly more emphasis on price. Moreover, among these newer European investigators, the absolute importance scores for price are comparable to the American scores.

### **Trading off for price**

The traditional model for investigator participation is no doubt still valid for many investigators, but the model fails to account for the central role that financial factors now play in the decision-making process for many investigators. Our survey suggests that the final grant price negotiated with European investigators will become more important and more aligned with the U.S. practice as the older, less price-driven investigators are replaced by younger, more price-driven ones. Understanding the importance of grant price and the trade-offs investigators make will become increasingly important.

Given the responses to this survey, informed sponsor companies may be able to balance price against other factors attractive to potential investigators. For example, although both U.S. and European investigators are price sensitive, they also appear willing to accept lower grant prices for the prospect of future work from a sponsor company or for an opportunity to test innovative products. The smart sponsor company will use this knowledge to manage its relationships with investigators more effectively.

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