

The Importance of Medical Innovation in an Investigator's Decision to Take Part in Clinical Trials

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The study draws upon a mail survey of 762 US investigators. Investigators provide a number of reasons for their participation in clinical trials, but this study underscores medical innovation as the most important stimulus. Among other reasons for participating in clinical trials, the prospect of additional financial remuneration plays an important role, especially for office-based investigators. Clinical investigators may be tempted to provide socially valued responses,

such as those relating to medical innovation, over more mundane considerations such as finances, as the reason for their taking part in clinical trials. Still, medical innovation figures prominently as a reason why investigators of all types participate in phase 3 clinical trials. This is important in understanding how to recruit experienced investigators, as well as physicians who may be potentially new clinical investigators.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Identify how to recruit experienced investigators, as well as physicians who may be potentially new clinical investigators.

Target Audience

This CME activity is designed for all involved in the design/implementation and analysis of clinical trials

INTRODUCTION

Research and development (R&D) productivity continues to present a major challenge for the pharmaceutical industry. R&D expenditures grow and new drug approvals decline (1), and late-phase clinical trials continue to be one of the costliest and most time-consuming steps in the R&D process. Moreover, while finding effective clinical sites is an essential part of successful late-phase clinical development (2), the number of US-based physicians who serve as clinical investigators has not kept pace with the increasing demand, even with the greater use of sites outside the United States (3,4).

The University of the Sciences in Philadelphia (USP) and TTC, llc are conducting an extensive

analysis of why some clinical trials finish faster than others. This analysis involves a number of dimensions including: the study and site attributes associated with faster clinical trial study completion; the role of outsourcing in drug development; and the profiles of clinical sites.

Knowing the demographics of clinical investigators and how they differ from those of the general physician population (3), we sought to establish, through a mail survey of US-based clinical investigators, why they chose to participate in clinical research. This article examines the reasons for their participation in clinical trials.

Previous research has pointed to the relative importance of innovation as a reason for a physician's participation in clinical research. In

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a conjoint trade-off analysis of more than 200 European and US clinical investigators, physicians indicated a willingness to work for a substantially lower cost per patient remuneration if they could be involved in a clinical trial of an innovative new compound (5). A subsequent multivariate analysis of actual grant payment levels for more than 3,000 US investigators showed that clinical investigators do accept a substantially lower cost per patient grant level when these physicians work on a novel first-in-class compound (6,7).

Financial remuneration in this study is an important consideration in many physicians' decisions to participate in clinical trials. However, the predominant motive for participation, among physicians of all types, is the prospect of contributing to innovative medical research. The potential implications for drug development of this finding are significant. Clinical grant payment levels alone most likely will not keep investigators involved in clinical trials, or encourage many other physicians to become active in clinical trials.

METHODOLOGY

THE QUESTIONNAIRE

In constructing the data collection questionnaire, we conducted a series of interviews with clinical investigators and drug development professionals. We pretested the questionnaire with several experienced clinical investigators and incorporated their suggestions into the final document.

Our questionnaire included a list of 12 reasons why an investigator might participate in a specific clinical trial. Respondents were asked

on a scale of 1–10, with 10 being very important and 1 not important at all, how significant each of the 12 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 items in five versions of the questionnaire.

A copy of the complete questionnaire can be found at the study website (8). In addition, the website provides the total set of respondent answers to the questions on that questionnaire (9).

THE SAMPLE

Using the Bioresearch Monitoring Information System File (10), we drew a random sample of 5,000 US investigators, stratifying by number of investigator statements (1572s) on record for a specific investigator. Nearly 50% of the physicians in the FDA 1572 database have filed only one 1572. We decided that it was not useful to have 50% of our sample come from this group of low-activity investigators, so we drew only 25% from this group. We were able to confirm the mailing addresses of 4,355 physicians, sending 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 did two mailings to the physicians with valid addresses, re-mailing to the investigators who did not respond to the first mailing. We received 762 usable questionnaires. We obtained 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 in completed questionnaires by the two strata. A somewhat lower percentage of investigators with one 1572 returned questionnaires, while a slightly higher percentage of

TABLE 1

Survey Return Rates for the 4,270 Sample and the 722 Completed Questionnaires		
Number of 1572s	Total Study Sample (%)	Completed Questionnaires (%)
1	25	21
2 or more	75	79
Mean 1572s	4.4	4.2

investigators with more than two 1572s returned a completed questionnaire.

STATISTICAL ANALYSIS

Throughout the article we indicate where differences are statistically significant at the .05 level or stronger. We also used factor analysis to determine whether the various individual reasons for participation were related to one another in some systematic way.

Factor analysis is a widely used and validated technique that examines the underlying factors that might explain the correlations between the individual items. This technique reduces a larger set of items to a smaller set. Factor analysis, which originated in psychometrics, is also used in economics, marketing, product management, and operations research. While answers to individual items are, at times, just answers to individual items, they may also be the result of a latent underlying structure. Factor analysis examines the interrelationships, or correlations, between all the individual items in a set of questions, and mathematically establishes whether such an underlying set of attitudes shapes the answers that participants provide to individual items. In other words, factor analysis provided this study with a perceptual map of the various reasons why an investigator might take part in a specific clinical trial.

We used a principle components analysis in the factor analysis, with a varimax rotation and Kaiser normalization. The model accounted for 55% of the variance (11).

FINDINGS

TWELVE REASONS FOR PARTICIPATION IN CLINICAL TRIALS

Table 2 presents the importance investigators attribute to the individual reasons for participation in a phase 3 clinical trial, with an average (mean) score reported for each item. In addition, the percentage of respondents who thought the item was very important is also presented. Very important is defined as receiving either an 8, 9, or 10 on the 10-point scale.

Three items received a score of very important from at least 55% of the investigators. All of the

items involved something about the drug being tested. For instance, the most important consideration for the investigators was the opportunity for a physician to work on a new therapeutic option for patients who were not responding to current treatments, or who had no approved treatment. Investigators also wanted to be sure that their site had experience in the study indication before agreeing to participate in a study. Also, many investigators indicated a willingness to participate in a clinical trial for an innovative drug, even if the research did not specifically relate to their patients.

A second group of reasons was critical to at least a third of the participants. Chief among this second set of reasons for participating in a clinical trial was the opportunity to share what the investigators learned from the study with physicians not involved in the clinical trial. Other reasons included the prospect of additional studies from the sponsoring pharmaceutical company, additional revenues for themselves or their organization, an investigator's experience with the contract research organization (CRO) or sponsoring pharmaceutical company conducting the clinical trial, and the opportunity to interact with other physicians in the same clinical trial.

A final set of reasons was very important to less than a third of the respondents: the level of startup funds offered by the organization running the study; confidence in other drugs already on the market from the sponsoring pharmaceutical company; whether a pharmaceutical company, rather than a CRO, was running the clinical trial; and whether a large multinational company was sponsoring the study.

THREE DIMENSIONS

Factor analysis of the 12 reasons for participation reveals that there are three underlying elements explaining investigators' reasons for participating in clinical trials. That is, these three dimensions form the latent structure for the responses to the 12 individual items. Most of the individual items are usually only associated with one of the dimensions. The individual items, and the respective strength of their association

TABLE 2

The Individual Reasons for a Physician's Possible Participation in a Clinical Trial Ranked by the Order of Importance to the Physicians Participating in the Survey		
	Very Important (%)	Mean Score
The opportunity to work with a potentially new therapeutic option for subjects who have not responded to available treatment, or for whom there are no approved treatments	87	8.8
My own site's experience working in the specific indication of the potential study	70	8
The chance to take part in innovative research, whether or not the research specifically relates to my patients	59	7.4
The opportunity to share with other physicians outside the clinical trial what is learned from my participation in the clinical trial	49	7
The prospect of additional studies from the sponsoring pharmaceutical company	47	6.7
To supplement the revenues/income of my practice/institution/department	43	5.8
My experience with the sponsoring company or CRO on previous work I have done with that company or CRO	43	6.4
The opportunity to interact with other physicians involved in the clinical trial	38	6.3
The amount of money required by my site to start the study until we receive payment from the organization running the study	30	5.7
My level of confidence in other drugs already on the market from that company	28	5.8
The sponsoring pharmaceutical company, rather than a CRO, is actually running the day-to-day operations of the study	19	4.7
A large, multinational pharmaceutical company is sponsoring the study	19	5

with the three factors, appear in Table 3. The important items are highlighted for each dimension. Across the table are the three factors, labeled medical innovation, financial considerations, and study sponsor and conduct. The data in the table are called factor loadings. These values indicate how strongly each individual reason for participating in a clinical trial relates to each of the three larger factors.

Factor analysis only provides a mathematical solution to how the various items relate to each other and does not label the individual factors. Items heavily associated with a factor are said to load on that factor. Items that load more heavily than others have a bigger explanatory role in understanding the commonality of the items associated with that factor. Only a review of the items associated with a given factor can provide a rationale for what the individual items may have in common. After reviewing the items associated with each factor, we developed the three factor names.

The concept of medical innovation ties together the items loading on the first factor. The five individual items on this factor are: the opportunity to work with new therapies to meet unfulfilled medical needs; the site's relevant medical experience for the study; the chance to work with other physicians involved in the clinical trial; the opportunity to share medical knowledge learned from participating in the clinical trial with other physicians not taking part in that trial; and the chance to take part in innovative research, whether or not the research specifically relates to the investigator's patients.

The second dimension contains financial considerations, including: the prospect of additional revenues; the site's experience with the company running the study; the amount of site start-up funds; and the prospect of additional studies from the sponsoring pharmaceutical company.

Five items loaded on the third dimension, la-

TABLE 3

Factor Analysis of the Importance Scores for the Individual Reasons for a Physician's Possible Participation in a Clinical Trial as the Importance Scores Relate to Each of the Factors			
	Medical Innovation	Financial Considerations	Study Sponsor and Conduct
To supplement the revenues/income of my practice/institution/department	-0.041	0.829	-0.039
My experience with the sponsoring company or CRO on previous work I have done with that company or CRO	0.153	0.426	0.557
The amount of money required by my site to start the study until we receive payment from the organization running the study	0.123	0.679	0.234
The sponsoring pharmaceutical company, rather than a CRO, is actually running the day-to-day operations of the study	0.074	0.193	0.59
The opportunity to work with a potentially new therapeutic option for subjects who have not responded to available treatment, or for whom there are no approved treatments	0.704	0.035	-0.045
A large, multinational pharmaceutical company is sponsoring the study	0.101	0.205	0.736
My own site's experience working in the specific indication of the potential study	0.186	0.109	0.446
The prospect of additional studies from the sponsoring pharmaceutical company	0.168	0.602	0.392
My level of confidence in other drugs already on the market from that company	0.075	-0.036	0.766
The opportunity to interact with other physicians involved in the clinical trial	0.63	0.033	0.412
The opportunity to share with other physicians outside the clinical trial what is learned from my participation in the clinical trial	0.765	-0.033	0.242
The chance to take part in innovative research, whether or not the research specifically relates to my patients	0.703	0.181	-0.032

beled study sponsor and conduct: the site's experience with the company running the study; whether or not the sponsoring pharmaceutical company is running the study; if the sponsoring pharmaceutical company is a large multinational company; the site's experience in the study indication; and the investigator's confidence in other drugs marketed by the sponsoring pharmaceutical company.

Factor analysis also provides a summary score on each factor for each physician, with a mean score of 0 and a standard deviation of 1 for each factor. These are called factor scale scores. The higher the final score, the more important that factor is for a given individual compared to the

other individuals in the study. In other words, each investigator has an overall importance, or factor scale, score for each of the three factors: medical innovation, financial considerations, and study sponsor and conduct.

Medical innovation was an equally important reason for all the major types of physicians in this study. Physicians with more 1572s are not statistically different from physicians with fewer 1572s. In addition, medical innovation remains a central consideration whether a physician is at a dedicated research site or not, and whether the physician is office based, hospital based, or located at an academic medical center. There are also no differences related to the size of

TABLE 4

Average Total Factor Scale Score for Each Factor for Each Type of Practice			
	Medical Innovation	Financial Considerations	Study Conduct and Study Sponsor
Office	-0.02	***0.177	***0.16
Academic medical center	0.05	-0.187	-0.21
Hospital	0.01	-0.29	-0.03

***Significant at the .001 level or stronger.

physician's institution or the number of full-time clinical research associates on a physician's staff. The desire to participate in innovative medical research drives physicians of all types in this study to take part in phase 3 clinical research. The results by type of practice are illustrated in Table 4.

Yet there are differences on the other two factors. Office-based physicians are the most likely to emphasize financial considerations in their decision to participate in clinical trials, while investigators in academic medical centers are the least likely to emphasize this factor. Office-based physicians are more likely to highlight financial considerations as the prospect of additional funds and the level of start-up funding. This was evident in the responses to the individual items that make up the financial consideration factor. For example, 50% of all office-based investigators think the prospect of additional revenues is a very important reason for participating in a specific clinical trial. In contrast, only 39% of investigators at academic medical centers feel that way, a percentage that declines to 29% for hospital-based investigators. The level of start-up funding is very important to 38% of the office-based investigators, but to only 23% of the academic medical center and hospital-based investigators.

There are also variations by the type of practice on the third factor: study sponsor and conduct. Again the difference ties to the type of physician practice. An illustration is the importance of previous experience with the organization conducting the clinical trial. Fifty percent of office-based physicians hold this to be a very important consideration compared to 37% and

26% of academic medical center and hospital-based investigators, respectively.

DISCUSSION

Investigators may have a range of reasons to justify why they participate in clinical trials, but this study underscores medical innovation as the most important stimulus. Simply put, many investigators welcome the opportunity to be a part of research for new treatments for their own patients and the patients of other physicians. They also enjoy the chance to interact with other investigators and to share what they learned from the clinical trial with other physicians who did not take part in that clinical trial. Of course, some clinical investigators may be tempted to provide socially valued responses, such as those relating to medical innovation, over more mundane considerations such as finances. Still, medical innovation figures prominently as a reason why investigators of all types participate in phase 3 clinical trials.

Financial considerations are important, especially for office-based investigators. These office-based investigators may be primarily concerned with considerations such as up-front payments since they do not enjoy the cash flow security of larger institutions.

Who is sponsoring and who is conducting the study are less important than medical innovation and finances as reasons for participating in a clinical trial. Testing an exciting new compound appears to be a greater motivator than the pharmaceutical company sponsoring the study.

The results of this study apply to phase 3, and probably phase 2, investigators. The motivation-

al factors may be different for physicians who concentrate on phase 1 or phase 4 studies. Also, the motivational factors may differ by variables not covered in this article, such as therapeutic area. Potential differences due to study phase and therapeutic area both merit further research.

While financial considerations will always be an important element in recruiting clinical investigators, medical innovation should not be underestimated as a motivating factor. There is no compelling evidence that paying investigators more either improves their study performance or influences their poststudy prescribing behavior of the study drug. Therefore, we might do better to view an investigator's finances from a business perspective of fair prices for good work, and not as way to motivate investigators to participate in a clinical trial.

An interest in medical innovation is probably crucial to recruiting investigators. It may also play a key role in finding new investigators, that is, physicians who have never participated in a clinical trial as an investigator. Even if these potential investigators have demographic, practice, and prescribing profiles similar to those of experienced investigators, the potential investigators will most likely also need to have an interest in medical innovation if they are to serve as effective clinical investigators. Taking part in a clinical trial is a demanding task. Rigorous procedures in all aspects of the undertaking, coupled with demanding record keeping, can put off potential investigators. Even if these potential investigators receive levels of compensation commensurate with the work involved in their first clinical trial, only those physicians with a fairly high interest in participating in innovative medical research may come back for a second clinical trial.

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