

Investigator Dissatisfaction with the Conduct of Clinical Trials

Organizations that incorporate what they learn from investigators into the design and management of their clinical trials will be better able to complete clinical trials of high quality in a timely fashion.

The performance of investigators at clinical trial sites plays a critical role in research and development productivity, which has declined in recent years, as evidenced by decreases in approved New Molecular Entities (NMEs) and in the number of New Drug Applications (NDAs) submitted to the U.S. Food and Drug Administration (FDA) for review and possible approval.¹ It is critical that we learn what operational concerns at investigative sites may be leading to this decreased productivity. Sponsor companies and contract research organizations (CROs) that understand the investigative sites' concerns will be better positioned to recruit and retain investigators; a site often decides to participate in a clinical trial based on its experience with the organization that manages the trial. Furthermore, understanding the sites' operational concerns can improve a study's initial design and execution. Clearly, organizations that incorporate what they learn from investigators into the design and management of their clinical trials will be better able to complete clinical trials of high quality in a timely fashion.

The University of the Sciences in Philadelphia and TTC llc are conducting an extensive analysis of why some clinical trials finish faster than others. This analysis examines the study and site attributes associated with completing clinical trial studies faster; the role of outsourcing in developing drugs; and the demographic, research, and practice profiles of clinical sites. Part of our analysis concerns what aspects of participating in clinical trials prove most challenging to investigators.

This paper, drawing from a mail survey of U.S. investigators, concludes that investigators' concerns center on financial management, drug safety reporting, and patient recruitment. Although these concerns are general throughout the investigator community, they are only concentrated to any statistically significant degree among those investigators most reluctant to continue participation in clinical research.

Background, Methodology, and Caveats

The survey questionnaire included a number of areas:

- Investigator levels of dissatisfaction with key operational aspects of conducting a clinical trial.
- Investigator willingness to continue as clinical investigators.
- The relationship of investigator demographics, practice profiles, clinical research experience, and willingness to continue conducting clinical research to investigators' level of dissatisfaction with the operational conduct of clinical research.

Table 1 Survey Return Rates for the 4,355 Sample and the 764 Completed Questionnaires

Number of 1572s	Total Study Sample (%)	Completed Questionnaires (%)
One	25	21
Two or more	75	79
Mean 1572s on file with the FDA during the most current three-year period	4.4	4.2

The study website contains a copy of the complete questionnaire² and provides the total set of respondent answers to all questionnaire items.³

This article describes the differences that are statistically significant at the .05 level or stronger. Gamma statistics and chi-square statistics were used for ordinal data, and one-way analysis of variance for metric data. Missing data never exceeded 4% of the questionnaire items for the respondents returning completed documents.

Investigators' concerns center on financial management, drug safety reporting, and patient recruitment.

Using the FDA 1572 database (the Bioresearch Monitoring Information System File), the project team drew a random sample of 5,000 U.S. investigators, stratifying by the number of 1572s on record for a specific investigator.⁴ Nearly 50% of the physicians in the FDA 1572 database have only one 1572 on file during the most recent three-year period (2005–07). We under-sampled this large group of one-time investigators, drawing only 25% of the sample from this subset. We mailed the other 75% to investigators with more than one 1572 on file.

In total, we were able to confirm the locations of 4,355 physicians for our questionnaire mailing. We sent two mailings to the principal investigators

with valid addresses, and followed our initial mailing with a second mailing to investigators who did not respond the first time. We received 764 useable questionnaires for a total response rate of 17.6% (see Table 1).

There may be an important bias in the physicians' response rate: As a total group, the investigators returning questionnaires may have a higher interest in clinical research than the physicians who did not return questionnaires. Members of the group returning completed questionnaires may also differ in such descriptive areas as demographics, the nature of their practice, or specialty area. IMS Health supplied these additional data for the total sampling frame,

enabling us to identify major differences between the total sampling frame and the sites returning completed questionnaires. IMS was able to supply these data for the 92% of the investigators whose addresses corresponded to their IMS Health records.⁵

The profile of investigators returning questionnaires is generally comparable to the total sample (see Table 2). Although we do not rule out possible biases in the returned questionnaires, we do not believe any biases, whatever their extent, obviate the value of the data.

Findings

We asked investigators to indicate if they were dissatisfied with a number of specific areas of conducting clinical trials. The items covered a wide range of activities involved in a typical clinical trial. We found that the three specific activities of greatest dissatisfaction were all related to the financial aspects of conducting clinical trials. Nearly one-third of the respondents stated that they have difficulty tracking costs against a budget, and a slightly smaller number point to their difficulties in develop-

Table 2 Investigator Demographics, Nature of Medical Activity, Nature of Practice, Specialty and Prescribing Level

Measurement Item	Total Sampling Frame	Investigators Returning Questionnaires
Investigator Demographics		
% Female	15	15
Average age	53**	54**
Nature of Medical Activity		
Direct patient care	88	84
Medical research and teaching	8*	13*
Nature of Practice		
Group practice	50	48
1 or 2 person practice	19	19
Specialty, Prescribing, and Research Experience		
Percent of investigators who come from the 20 largest practices	91	91
Prescribing decile	3.4	3.3

* = .05 significance.

** = .01 significance.

ing an accurate study budget against which to track actual costs. A quarter of the participants expressed a continuing concern about the timely collection of invoices against milestones.

According to one midwestern investigator, "Internal billing and collection processes are difficult and payment from sponsors is not always timely." Similarly, a Pacific Coast physician wrote, "Based on current industry practices, it is almost impossible to track milestone payments to ensure that all study visits/procedures are being reimbursed."

In recent years, the popular media and the scientific and medical literature have focused intensively on drug safety and specifically on marketing.⁶⁻⁸ In this study, we were struck by the number of investigators who expressed their concern with the processes for reporting serious adverse events (SAEs) in clinical trials. More than one-quarter of the sites believe this is an important concern in conducting clinical trials.

The three specific activities of greatest dissatisfaction were all related to the financial aspects of conducting clinical trials.

Furthermore, our findings bear witness to the fact that drug development professionals consider patient recruitment to be a major obstacle in completing successful clinical trials in a timely manner.⁹ A Washington, D.C., investigator succinctly stated the concern by noting, "Difficulty in recruiting participants is the major snag in performing these studies." Similarly, a Texas physician wrote, "We have been participating in clinical trials since 1991, and if there was anything that is difficult for us, it is patient recruitment. I would like to have a better system in place for recruitment. Otherwise, we enjoy research."

In another area, many sponsor companies make use of CROs to conduct clinical trials.¹⁰⁻¹⁵ For example, sponsor companies report that more than 64% of all their Phase I-IV studies have a CRO involved at some stage of the project.¹⁶ Some investigators may prefer to work directly with the sponsor pharmaceutical company. However, most do not care whether they work with a sponsor company or a CRO.¹⁷ In this research, investigators who do a lot of work with CROs do not report higher levels of dissatisfaction than investigators who undertake relatively less work with CROs; we find no notable difference in the response patterns when we take into account the amount of work an investigator does with a CRO.

Investigators are less dissatisfied with other areas that the study explored. For example, about one in 10 is dissatisfied with the amount of time the study monitor spends at the site. Even smaller numbers mention being unhappy with tracking clinical trial supplies and study closeout (see Table 3).

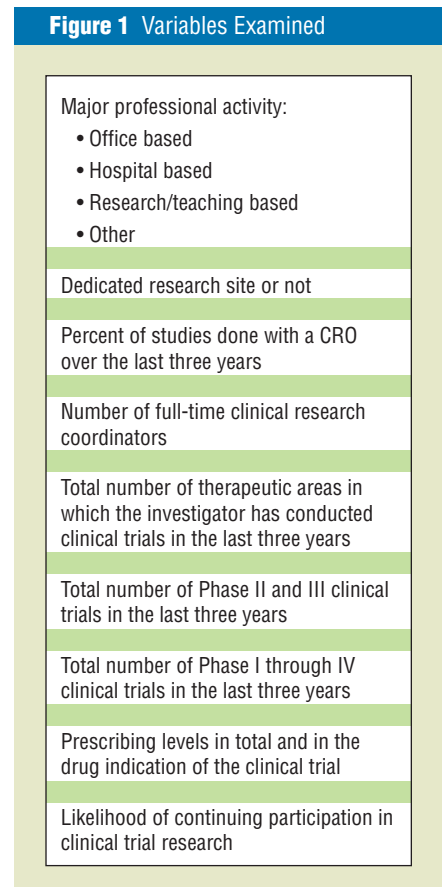
Finally, using bivariate correlations and multivariate models, we examined whether any subset of investigators indicated consistently higher or lower levels of dissatisfaction. The variables appear in Figure 1. With one exception, dissatisfaction was not higher in any investigator subgroups. For example, dedicated research sites were no more dissatisfied than nondedicated sites—even with the financial items. The response pattern for office-based investigators did not differ consistently from investigators located in hospitals or based in teaching and academic medical centers.

On several items, sites conducting fewer Phase II and III clinical trials were more dissatisfied. Their concerns included tracking clinical trial costs against budget, accurately forecasting the study budget, and recruiting and retaining patients. However, on only one item—accurate study budget forecasting—were less experienced investigators significantly (statistically) more dissatisfied. Moreover, on some of the other items, sites with more Phase II

Tracking clinical trial costs against the budget	30
Accurately forecasting study budget	27
Timely collection of billables against milestones	26
SAE reporting	26
SAE follow-up	5
Patient recruitment	22
Patient retention	4
Study monitor time at sites	12
Tracking clinical trial supplies	9
Study closeout	8

and III experience were the more dissatisfied set of investigators.

One subgroup of investigators did demonstrate higher levels of dissatisfaction. Predictably, investigators who indicate that they probably, or definitely, will not continue to do clinical



trials are less happy with many of the specific operational activities associated with clinical research (see Table 4). Only 5% of our study investigators did not plan to take part in future clinical trial research. These investigators were more troubled than other investigators with some of the clinical research processes, including forecasting and tracking costs, recruiting and retaining patients, the time the monitor spent at the site, and closing out the study. They were less concerned than other investigators with cash flow and patient safety issues.

Discussion

Cautionary Notes

Mail surveys may be particularly susceptible to bias. Investigators returning questionnaires in this study may, for instance, have a greater interest in conducting clinical trials. However, in comparing investigators returning questionnaires with those not returning questionnaires, we found far more similarity than dissimilarity on key demographic and practice characteristics.

These data cover the United States only. We are conducting comparable surveys in other geographic areas, although data protection laws in many of them prohibit third-party organiza-

tions from supplying physician-specific data to research organizations.

More on Money

Investigators of all types, as we might expect, are concerned about financial issues, ranging from developing accurate forecasts to cash flow. For example, those in office-based practices are not significantly more dissatisfied with the financial aspects of clinical trials than those working in hospital settings. We found that financial remuneration is a more important reason for these investigators to take part in clinical research than it is for hospital-based investigators or physicians in teaching hospitals or academic medical centers.¹⁸

We should distinguish between the general level of financial remuneration and the mechanics of financial management. It is doubtful that many investigators, or few others involved in new drug development for that matter, feel they are paid too much to conduct clinical trials. Investigator participation in clinical trials, in particular, is often demanding from medical and administrative perspectives, yet many sites of all types appear to continue to struggle with the operational issues of financial management.

From time to time, some managers in sponsor pharmaceutical companies

indicate an understanding of the operational financial issues faced by sites, as well as the possible financial management help that sponsor companies might be able to offer sites, although little is usually done. Clinical development professionals are often simply too overwhelmed by their own operational demands to be able to expend time or resources to assist sites with these financial management challenges. Moreover, the incremental return to a specific company from helping sites with financial management may not be immediate enough.

Many sites of all types appear to continue to struggle with the operational issues of financial management.

It is probably of great value to individual sponsor companies to work with sites to improve their financial management, both as a way to maximize the value of the overall working relationship between the site and the sponsor company, as well as to make the general prospect of conducting clinical research at new and existing sites more attractive. At a minimum, professional drug development associations could increase the level of financial management training made available for investigative sites. Organizations involved in drug development would do well to expend the time to understand the types of processes and systems sites need to improve patient identification and patient enrollment.

The SAE Factor

Also noteworthy is the uneasiness among investigators about the reporting systems associated with SAEs. A significant minority of clinical investigators in our study are troubled by SAE reporting systems. They may be more sensitive to the general issue because medical professionals, regula-

Table 4 Clinical Trial Activity Dissatisfaction by the Likelihood of Continuing Conducting Clinical Trials

Area of Dissatisfaction	Investigators Likely to Continue	Investigators Not Likely to Continue
Tracking clinical trial costs against the budget	29	*37
Accurately forecasting study budget	27	35
Timely collection of billables against milestones	26	21
SAE reporting	26	21
SAE follow-up	5	11
Patient recruitment	21	*38
Patient retention	4	*13
Study monitor time at sites	11	*21
Tracking clinical trial supplies	8	10
Study closeout	8	**21

* = .05 significance.

** = .01 significance.

tors, officials, and the general public have given it considerable attention. For example, a recent Institute of Medicine report highlighted the difficulty of anticipating possible drug safety issues with marketed drugs based on the relatively small number of patients taking part in clinical research studies. In addition, the FDA has adopted a new organizational structure that separates the approval of new drugs, including examinations of the safety of proposed products, from the monitoring of safety for drugs already on the market.¹⁹

Pharmaceutical companies must understand in greater detail the nature and depth of the concern about SAE reporting that has surfaced in this survey.

Whether or not this heightened public attention has influenced the investigator's evaluations, we did find them to be concerned about SAE reporting, and this may be an increasingly large issue for sponsor pharmaceutical companies. The physician is critical in the medical decision for a patient's participation in a clinical trial. Physicians who feel at all uncomfortable with the issue of drug safety reporting may be reluctant to allow the participation of their patients in a clinical trial. Similarly, a physician may express this concern to other doctors who may be contemplating taking part in later-phase clinical research. Pharmaceutical companies must understand in greater detail the nature and depth of the concern about SAE reporting that has surfaced in this survey; it represents an especially important area of future research for this project.

Finding Warm Bodies and More

Recruiting patients is an issue for a significant minority of investigators. The

difficulty in patient recruitment may arise, on the one hand, from unrealistic patient inclusion/exclusion criteria. In this case, there is little else that sites can do than to work with sponsor companies to alter the criteria for a particular study. Pharmaceutical companies themselves will have to find more effective ways to test inclusion/exclusion criteria before beginning to recruit sites and enroll patients. On the other hand, sites are often limited by their own patient records in finding potential patients for clinical trials.

Other operational issues are less troublesome. For instance, only one in 10 sites was disturbed by the time site monitors spend at the study site.

In general, the pattern of dissatisfaction is comparable across the investigators in this study. However, based on an admittedly small group of investigators, those who believe they will most likely not continue with clinical research were more dissatisfied than other investigators on a range of activities.

Conclusion

Conducting clinical trials is an increasingly complex task. In our study, investigators of all types have comparable levels of uneasiness about key activities in conducting clinical trials. Understanding these investigator concerns will help the perceptive sponsor company or CRO to attract and retain the most valued investigators. Moreover, understanding the sources of investigator anxiety will highlight the areas where effective management can introduce improved clinical trial design and management processes.

Acknowledgement

The author thanks Dan Beaudry, Jena Jankosky, and Jesse Glass for their help in designing the questionnaire, collecting the data, and processing the responses.

References

1. U.S. Government Accountability Office. 2006. New drug development: science, business, reg-

- ulatory and intellectual property issues cited as hampering drug development efforts. *Government Accountability Office* 2006; GAO-07-49.
2. University of the Sciences in Philadelphia and TTC's Investigator Site Survey: www.ttc-llc.com/Surveys/Profiles_of_Clinical_Invs_Questionnaire.pdf.
3. University of the Sciences in Philadelphia and TTC's Investigator Site Survey Results: www.ttc-llc.com/Surveys/Profiles_of_Clinical_Invs_Results.pdf.
4. U.S. Food and Drug Administration database.
5. IMS Health, Inc. Plymouth Meeting, Pa.
6. Leiden J. Canaries. 2008. Coal mines and the drug supply. *Nature Biotechnology* 26(6): 624.
7. Keyhani S. 2008. FDA drug review deadlines: a safety concern? *Journal of Clinical Outcomes Management* 15(5): 224.
8. Anderson G et al. 2008. Newly approved does not always mean new and improved. *Journal of the American Medical Association* 299(13): 1598.
9. Cutting Edge Information. Clinical Operations: Accelerating Trials, Allocating Resources & Measuring Performance. 2006. Available at www.cuttingedgeinfo.com/clinical-trials.
10. Kermani F, Langer E. 2007. Outsourcing is key to future pharmaceutical R&D strategy. *Pharmaceutical Technology Europe* 19(3): 14-5.
11. Wadman M. 2006. The quiet rise of the clinical contractor. *Nature* 411(7089): 22-3.
12. Copestake A. 2006. The value of CROs in drug development. *Pharmaceutical Technology Europe* 18(11): 59-61.
13. Vogel J, Getz K. 2006. Successful outsourcing of clinical drug developments. *BioExecutive International* 2(6): S30-8.
14. Porter W, Krivacic S. 2005. The CRO advantage: outsource clinical trials to launch biotech development success. *Biopharm International* 18(6): 59-60, 62, 70.
15. Getz K. 2007. CRO shifts in the outsourcing market. *Applied Clinical Trials* 16(5): 35-6, 38.
16. Glass H. 2007. Outlook for outsourcing. *Good Clinical Practice Journal* November: 21-24.
17. Glass H. In press. Investigator attitudes toward participation in CRO managed clinical studies. *Clinical Trials*.
18. Glass H. 2008. The importance of medical innovation in an investigator's decision to take part in clinical trials. *Drug Information Journal* 42: 537-43.
19. Schneider ME. 2006. FDA plans reorganization aimed at improving drug safety, development. *Clinical Psychiatry News* 34: 11, 12-2. **ACRP**

Harold E. Glass, PhD, is professor of health policy at the University of the Sciences in Philadelphia and senior research fellow at the Centre for Evidence Based Policy, Kings College, University of London. He also is the founder of DataEdge, LLC, which he sold in 2001 to IMS Health. He currently owns TTC llc, whose databases, GrantPlan® and CRO CostPro™, are the largest clinical grant and CRO costs databases available. He can be reached at h.glass@usp.edu.