

## **STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies**

### **Chapter 10. Maximizing Investigator Motivation**

*This article is the tenth part of a 15-part series from STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies by Hugo Stephenson, MD, President, Strategic Research & Safety, Quintiles.*

Investigator motivation is a critical factor in the operational success of a clinical study. While many factors that influence investigator motivation are outside the scope of study design or implementation—such as an investigator's natural interest in research or the number of other competing research studies in the same therapeutic area—there are a handful of key study attributes that measurably and significantly drive investigator interest.

The attributes of a study that contribute to investigator motivation, from most to least important, are (1) the benefit to the patient, (2) scientific immediacy, and (3) financial compensation. Optimizing these attributes to maximize investigator motivation can be a simple and efficient way to save on external site support costs, and can result in a self-driving study with a momentum that allows for increased design complexity.

#### **Benefit to the Patient**

The greatest driver by far of investigator motivation is the benefit that accrues to patients who participate in a study. Whatever their level of research experience, investigators are physicians concerned primarily with the improvement of patient care. All studies involve some level of inconvenience for a patient, even if this is only additional data collection. Many studies involve multiple additional visits to a clinic and additional tests, some painful. Not many patients like being guinea pigs for the sake of it. It is much easier, and more pleasant, to offer study participation to a patient as a chance to obtain a benefit, rather than in the context of a patient's duty to science and research. If insurance or government programs are not yet paying for drugs or procedures, providing them free of charge can be a very strong driver of patient recruitment.

Patient benefits usually take the form of one or more of the following:

- Access to treatment that is not yet approved
- Access to treatment that is not reimbursed
- Access to tests that are not widely available
- Access to tests that are not reimbursed
- Access to services that are not reimbursed
- Financial compensation

Investigators are highly motivated to participate in Phase II and III studies, which offer patients access to treatments not yet approved by regulators. Many investigators, particularly in oncology, rheumatology, and infectious diseases, participate in earlier phase research to offer patients access to experimental treatments. It has become increasingly difficult for sponsors to recruit patients for studies on experimental treatments not clinically or pharmacologically different from other products already available.

Those planning strategic research activities in Phases IIIB and IV should be mindful of designing studies to maximize patient benefit. A pre-approval Phase IIIB program has a good chance of strong enrollment by offering product that is not yet available. Once approval is obtained, expect that investigator and patient motivation will rapidly diminish. If the workload of the study is not designed to taper off in line with market approval, study managers will need to use a significant amount of external support at the tail end of a study to compensate. The same principle applies for studies started immediately after marketing approval but before reimbursement. External factors can rapidly change the relative benefit of a study to patients, and thus can indirectly but significantly influence investigator motivation and study performance.

### Scientific Immediacy

Of next greatest importance to investigator motivation is the scientific immediacy of the study. The investigator will benefit from knowing how relevant and timely the study's scientific questions are to his or her day-to-day practice. Investing a little time to produce site-recruitment materials, protocol synopses, and protocol introductions that highlight the clinical value of the study will pay off many times over in the course of the project.

Scientific immediacy should not be confused with absolute scientific importance. For example, a regulator or sponsor may be keen to demonstrate the safety of a cholesterol-lowering drug in pregnancy—a valid question of broad scientific importance. Because general practitioners do not prescribe cholesterol-lowering medication to pregnant women on a daily basis, however, the immediate application of this research to their practice may not seem significant. On the other hand, obstetricians who specialize in the management of diabetic patients with high cholesterol may recognize a far greater scientific immediacy of the study.

Scientific immediacy also implies a timeliness of analysis. A five-year study, without an interim analysis, is far less motivating than a one-year study with regular interim analysis and communication of results, even if the research objective of the one-year study has much less clinical significance.

Scientific immediacy, like patient benefit, is an important attribute that can be affected by external factors over time. In designing long studies, one should recognize that scientific

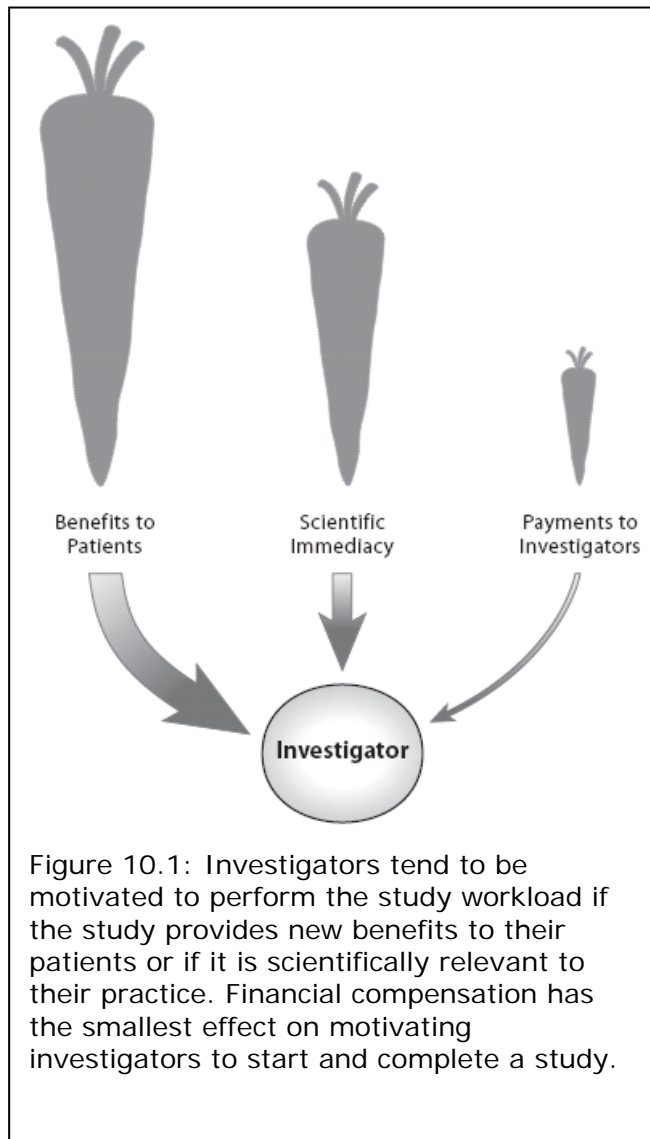


Figure 10.1: Investigators tend to be motivated to perform the study workload if the study provides new benefits to their patients or if it is scientifically relevant to their practice. Financial compensation has the smallest effect on motivating investigators to start and complete a study.

Quite recently, a sponsor started a large observational study for a marketed product. The sponsor did not provide the investigational drug, reasoning that it was available through commercial channels, but investigators were paid approximately \$100 per visit to complete monthly safety review forms. This study had difficulty recruiting from day one because it had limited scientific immediacy and no short-term patient benefit. After recognizing these problems, the sponsor began to provide study drug through a pharmacy coupon program (valued at approximately \$100 a month) and eliminated investigator payments to remain budget neutral. Even though investigators no longer received payment, patient recruitment accelerated so significantly that the study completed ahead of schedule.

immediacy decreases over time. Design the study so that patient benefit, financial incentives, or external support increase, or study workload decreases, to compensate for this change.

Sponsors frequently ask me whether they can use sales force or medical liaisons to perform some of the clinical workload. My response is simple. Even ignoring the possible legal and regulatory dangers of having sales representatives participate in studies, the talents of a sales representative are better used elsewhere. Sales representatives and medical liaisons can be more effective in facilitating clinical operations by enhancing the scientific immediacy of a study rather than by helping with the study process itself.

For example, recruitment for a study is significantly enhanced if the media has recently highlighted a related healthcare or clinical issue. Physicians are more likely to recruit patients into a study investigating the

relationship between dose at the onset of aura and severity of migraine if sales representatives present data suggesting that many patients with crippling migraine do not receive maximum doses of therapy. Similarly, a medical education campaign focused on increased cardiovascular risk in association with high cholesterol will measurably improve site participation in a study investigating the safety of a lipid-lowering treatment.

Most sponsors will be running a range of educational and communication activities in parallel with their Phase III B and IV research. Using these activities to highlight a health issue being tackled by a parallel research study will create significant synergy between the two programs without requiring a direct linkage.

### Financial Reward

Surprisingly, for many investigators, payment is not a powerful driver of motivation. Investigators find it hard to enroll patients on the basis that their participation will be lucrative for the site.

Although it is often easier to offer more money, it may be more effective to change the research direction of the study, simplify it, or add features that may increase the benefit for patients.

While some payment is usually necessary to cover the fixed site costs associated with a study, it is my experience that spending an additional



Figure 10.2 Clinical researchers. An essential part of running a trial successfully is motivating investigators.

\$100 on site payments is less motivating than offering \$20 of additional value to the patient. I have been involved in many successful studies that required little external support and no payment to investigators at all. They enrolled between 10,000 and 60,000 patients on the basis of strong patient benefit and interesting science.

### **Conclusion**

It is my strong recommendation that teams design studies to minimize workload, maximize patient benefit, and promote scientific immediacy before performing a basic feasibility study to determine the investigator-fee structure necessary to achieve the desired site behavior. Not only will this approach save significant amounts of money for the sponsor, but in regions where increased scrutiny is applied to research payments made in parallel with commercial activity, a lower, well-documented, and justified fee structure could protect against enormous penalties (see the appendix).