

The Uphill Path to Successful Clinical Trials

Keeping Patients Enrolled

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INTRODUCTION

The path to drug approval, long known to be arduous, appears to be growing more difficult. The incline of one essential stretch of the journey, the one that provides lifeblood data and that rests on enrolling and keeping patients in clinical trials, has become particularly steep. *The Prevention and Treatment of Missing Data in Clinical Trials*, a 2010 publication of the National Academies Press (NAP),¹ cites patient dropout rates in phase 3 clinical trials that “can often be very substantial,” sometimes more than 30%. With an increasing emphasis on *quality data* (longer-term and outcome-based), the specter of huge research expenditures failing to convincingly answer safety and efficacy questions makes a case for paying heightened attention to all the logistics to ensure that the trials are successfully fulfilling their missions.

To reduce the frequency of dropouts, the NAP publication suggested that clinical trial managers limit participants’ burdens and inconvenience during the data-collection stage by minimizing the sheer number of visits and assessments, by collecting only the information needed at each visit, and by making case report forms easier to use.¹

USER-FRIENDLY?

These logical and practical suggestions, unfortunately, are not consistent with the reality of the research environment. The justifiable need of sponsors to make their research investment count and for the data to be available for all planned and even potential future subanalyses generates stiff demands on research sites and on the patients participating.

The Kenneth I. Kaitin 2008 *Impact Report*² from Tufts University stated that over the previous decade, the overall duration of clinical trials increased by 70%, the burden on staff workers went up 67%, the number of trial protocol procedures expanded by 65%, and the average case report form ballooned from 55 to 180 pages. At the same time, pages were added to consent forms and the forms became more complicated.

From the regulatory side, the FDA has begun questioning the reliability of predicting long-term outcomes through the use of surrogate endpoints. In his *Forbes Magazine* blog, called “Drug Truths,” John L. LaMattina, PhD, who retired as president of Pfizer Global Research and Development in 2007, sided with the FDA’s demands for longer-term studies and for endpoints based on hard outcomes rather than surrogate endpoints.³

As an example, approval of the widely prescribed antidiabetes agent rosiglitazone (Avandia, GlaxoSmithKline), he noted, was based on its impressive ability to lower blood glucose levels. Long-term postmarketing studies, however, revealed no reductions in adverse cardiovascular events. That evidence has been accompanied by other well-known surprises with respect to supposedly valid surrogate endpoints: tumor shrinkage was shown

not to enhance survival, bone stabilization did not prevent fractures, and increases in high-density lipoprotein-cholesterol (HDL-C) levels failed to reduce heart attacks.

These findings, Dr. LaMattina suggested, despite his “Big Pharma” pedigree, constitute a mandate for the FDA to make more stringent demands. In a January blog entry, he wrote:³

... [The] FDA has been requiring companies to run outcome studies *before* granting drug approval, particularly for chronic disease drugs intended for long-term use by patients. This policy is costly for companies, as these studies can cost anywhere from \$300–800 million, depending on the scope of the trial. But it is proving necessary, as shown most recently with Merck’s Tredaptive [extended-release niacin/laropiprant], a drug designed to reduce heart attacks and strokes but which was shown in a major clinical trial (HPS2-THRIVE*) with 25,673 patients to provide no benefits over standard therapy and might even be harmful.

This emerging need for longer-term outcome data collection and its cost naturally spur the work of building long-term relationships among research institutions and clinical trial participants, including patients who drop out for any possible reason.

AN ATTITUDE PROBLEM?

Another factor darkening the experience of patients in clinical trials is a general devolution of public confidence in health care institutions. Knowing which misgivings haunt the minds of prospective clinical trial participants and being prepared to reassure patients are professional obligations for those charged with gathering quality data. A variety of surveys reviewed by The Center for Information and Study on Clinical Research Participation (CISCRP) reveal conflicting attitudes.^{4–9} Although most Americans think that clinical trial research is of great value (71% and 63% in two separate polls) and 57% said that they would be likely to participate in clinical research, 40% of those surveyed responded that they would not participate.

In a 2007 poll of 1,726 adults in the U.S., many expressed “somewhat” or “very strong” mistrust of the FDA in 27%; only 31% believed that the FDA effectively ensured drug safety.⁶ (The percentage of respondents with this belief had been 56% only 3 years earlier.) Nearly half of Americans polled expressed distrust of the Capitol Hill officials charged with overseeing regulatory and drug development processes.⁶

That same distrust (42%) also applies to pharmaceutical and biotechnology companies. The poor ratings they received, 39% in 2007, were far worse than the 19% of poor ratings received a decade earlier. A 2008 survey showed 44% of Americans viewing pharmaceutical and biotechnology companies unfavorably, and 27% did not trust them to provide reliable

*Heart Protection Study-2: Treatment of HDL to Reduce the Incidence of Vascular Events.

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information about adverse drug effects and safety. Only 55% expressed confidence that information would be disseminated to the public quickly if safety concerns about a drug were discovered.

A disturbing question—Would your doctor expose you to unnecessary risk in a clinical trial?—was answered *yes* by 25% of those queried. Furthermore, in a CISCRP survey, instead of finding that people consider participating in a clinical trial to be a noble endeavor, many felt that people participated because they were “very sick without any other options” or were “looking to make money.”⁹ One-third responded that they did not admire people who volunteered for clinical trials.

DOING IT RIGHT

Listing such obstacles highlights the need for a highly conscientious, scrupulously well-thought-out professional approach to patient enrollment and retention. A genuine partnership has to be created and sustained among sponsors, research sites, and research subjects. The NAP publication makes recommendations toward that end,¹ suggesting the use of direct data capture (eliminating some clinic visits); bolstering participant incentives for enrolling and staying in trials; careful selection of study sites and investigators; good pre-study training and on-study reinforcement of the importance of data gathering; and an emphasis on continued data collection from subjects who discontinue study treatment.

Investigators and research staff, in their training, should be prepared to make use of the informed consent process to create awareness and understanding by enrollees that their participation includes a commitment to the trial, regardless of the treatment they receive or their possible eventual withdrawal from the study.

For more than a decade, a mini-industry has grown up around supporting patient enrollment, and that industry has quickly seen its role extend to improving patient retention. Various tools have been developed to strengthen patients' identification with and commitment to the research project and to coordinate and integrate the multitudinous tasks of patient scheduling and testing.

COMPENSATING PARTICIPANTS

Although efforts to prevent subjects from withdrawing from a study must stop short of coercion, investigators and site personnel can go far in addressing participants' concerns about the conduct of a trial. Also, it is acceptable to offer financial incentives to investigators for continuing to collect data on patients who withdraw; it is also appropriate to identify sites where data collection has become deficient and then bring additional training or other direct remediation to these sites.

The NAP explicitly states that paying for voluntary participation in a clinical trial is considered ethical, as long as the institutional review board (IRB), in accordance with the Code of Federal Regulations, “ensures that the compensation is neither coercive nor at the level that would present undue influence.”¹ Cash payments can be slightly back-loaded, with a small proportion held back as an incentive for the trial or the data to be completed. Compensating subjects for taking risks is common and generally acceptable as long as the practice

does not become coercive. It is also generally considered ethical to pay patients who have discontinued study medications for return visits, because such visits carry no or minimal risk to the participant. Judged as similarly ethical, the distribution of study-branded gifts can enhance participants' engagement with the trial.¹

The picture, however, must be balanced by a less liberal view. In a session presented at the Cardiovascular Research Technologies meeting in February, C. Michael Gibson, MD, Chief of Clinical Research at Boston's Beth Israel Deaconess Medical Center, Cardiovascular Division, said:

You cannot lead patients to believe that there is a benefit to them personally from participating in the study or provide any monetary incentive to patients for their participation. You can obtain IRB approval to reimburse patients for travel expenses and parking expenses.¹⁰

IDENTIFYING PROBLEMS

The Prevention and Treatment of Missing Data in Clinical Trials also endorses efforts by investigators and site personnel to collect patient information that can be used to guide them as to which subjects are at risk for dropping out.¹ This kind of intelligence gathering can provide both general insight and opportunities for excluding such patients from a study. The report presents some potential problem areas affecting patients' initial and ongoing participation, namely concerns about time commitments, transportation and child care arrangements, the need for reminders, relationships with staff members, anxiety about blood draws or other procedures, adverse drug effects, and misgivings about a medication's efficacy.

SUPPORT FROM THE START

Sponsors, research coordinators, and investigators can be taken by surprise when a combination of intensifying factors that impede the fulfillment of research aims (i.e., patient resistance, complex protocols, extended follow-up periods) leads to high dropout rates and seriously underpowered data analyses, said Scott Connor, Vice-President of Marketing for Acurian, in an interview. Fixing the problem late in the game can be expensive and impossible to guarantee. Third-party support, he suggested, should be included in the beginning. Acurian, based in Horsham, Pennsylvania, has supported more than 450 clinical trial protocols since the company was founded in 1998.

The other key, he said, is the flexibility to adjust techniques to fit the particulars of the trial details and protocol. For example, an opportunity to communicate with patients can be created when there are large gaps between patient visits or when a pharmaceutical under study produces adverse effects that justify increased monitoring. He commented:

The formula for effective third-party retention services is direct and simple. In a manner that is customized and individualized for the study protocol, the site, and the patient, organize schedules and tasks with sophisticated software, track progress to identify retention issues *before* they become intractable, take on administrative tasks in a manner that encourages stronger bonds between site staff and patients, and reduce the site staff's overall workload.

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CONCLUSION

Keeping patients in clinical trials to ensure successful and long-term data-gathering requires careful planning and proactive strategies. Attention needs to be directed to the individual needs of patients and site staff in relation to specific demands of the research protocol.

REFERENCES

1. National Academy of Sciences. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, D.C.: National Academies Press; 2010. Available at: www.nap.org. Accessed March 1, 2013.
2. Kaitin KI, ed. *Impact Report: Growing Protocol Design Complexity Stresses Investigators, Volunteers*. Vol. 10, No. 11. Boston: Tufts Center for the Study of Drug Development, January–February 2008. Available at: <http://csdd.tufts.edu>. Accessed March 1, 2013.
3. LaMattina J. Large clinical trials important but JAMA article recommendations are off-base. *Forbes*, January 24, 2013. Available at www.forbes.com. Accessed March 1, 2013.
4. Research!America. *Transforming Health: Fulfilling the Promise of Research*. Alexandria, Va.: The Charlton Company; 2007. Available at: www.researchamerica.org. Accessed March 1, 2013.
5. Leo J. Shapiro & Associates. *New LJS Healthcare Study Finds Broad Consumer Acceptance of Behind-the-Counter Drugs*. Chicago: LJS Healthcare; 2007. Available at: www.ljs.com. Accessed March 12, 2013.
6. Harris Interactive. Lack of trust in both FDA and pharmaceutical companies makes drug safety a concern for many. *HealthCare News* 2007;7(6):1–5. Available at: www.harrisinteractive.com. Accessed March 1, 2013.
7. Kaiser Family Foundation. *Public Opinion Spotlight*, May 2008. Available at: www.kff.org/spotlight. Accessed March 1, 2013.
8. Braunstein JB, Sherber NS, Schulman SP, et al. Race, medical researcher distrust, perceived harm, and willingness to participate in cardiovascular prevention trials. *Medicine (Baltimore)*, 2008;87(1):1–9.
9. Center for Information and Study on Clinical Research Participation (CISCRP), 2006. Available at: www.ciscrp.org. Accessed March 1, 2013.
10. Gibson CM. Tips on how to increase screening and enrollment into clinical trials. Cardiovascular Research Technologies meeting, Washington, D.C., February 25, 2013. ■