

# Trends in Subject Recruitment 2009

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## Subject Recruitment: Then and Now

When I worked for *Pharmaceutical Executive* magazine about 20 years ago, pharma companies contracted with investigators at academic research centers. Upon joining *Applied Clinical Trials* in 1994, industry changes and CROs were moving clinical trials in new directions.

The first clinical research conferences I attended in the mid-1990s offered a few subject recruitment workshops for clinical coordinators who recruited locally. Later in the '90s, exhibition halls occasionally had a rudimentary booth or two staffed by people from small companies that specialized in advertising trials in local newspapers and on radio and television stations.

During the past decade, subject recruitment and retention has blossomed into a major business. The exponential growth of information technology has been one driver—perhaps the major driver—of that growth. People with rare, debilitating, or life-threatening conditions browse the Web in search of relief.

Only a few short years ago, the ability to forecast trial enrollment with anything approaching today's accuracy was below the horizon. Amassing the performance metrics needed to model those predictions was a time-consuming roadblock.

Today's ubiquitous high-speed computing provides easy access to global communication, real-time data, and faster data analysis. Clinical trials managers embrace sophisticated marketing and business models. It is not surprising, then, that innovative approaches to subject recruitment and retention emerge—and to see them described in "Trends in Subject Recruitment 2009."—**Jane Ganter**

Thoughtful evaluation of performance metrics can lead to best recruitment practices.

# Measuring Recruitment Performance

Tony Hursey

All stakeholders strongly desire reliable ways to accurately measure and compare the relative cost-effectiveness of patient recruitment methods. However, there is currently neither a widely held consensus nor an established set of standards defining what the appropriate measures should be for various recruitment methodologies.

Establishing and adopting standard patient recruitment metrics for this would not only provide common terms that would aid and clarify related communications and enable accurate cross-study comparisons, but it would also support the development of recruitment performance benchmarks that can be used to enhance best recruitment practices for future trials.

To this end, suggested recruitment performance measures are proposed here for both direct and indirect outreach methods. Key planning and operational requirements to enable the capture analysis and comparison of patient recruitment metrics are also outlined.

## An Elusive Goal

Capturing evaluable patient recruitment metrics should in theory be a simple proposition. In practice, it has proven to be surprisingly elusive.

Part of the issue with the ability to capture metrics stems from the fact that patient recruitment programs can come in many different forms and combinations, depending on the types of protocols, indications, and patient demographics they support, and very importantly, where the study is conducted. Furthermore, individual recruit-

ment tactics themselves have varying levels of measurability.

As a rule, centralized direct-to-patient outreach tactics lend themselves to the collection of trackable metrics. That is because responses to outreach are received through a measurable avenue, typically either a phone call to a contact center or a click of an online advertisement that takes you to a dedicated study Web site.

The impact of less direct—but important—tactics, however, such as using patient and/or physician directed recruitment materials (e.g. brochures, posters, study fact sheets, etc.), are by their nature much harder to definitively measure.

There are also measurable tactics that fall between these two ends of the spectrum. Recruitment specialist site support, for example, cannot generally be directly tied to the enrollment of specific participants, but does allow intrastudy comparisons either to a baseline presupport period or between sites receiving recruitment specialist support versus sites receiving no such support.

Beyond outcome measurability, availability of complete performance data on measurable tactics continues to be a challenge for some clinical trials. Despite the recognized importance of metrics, the primary barrier to not having evaluable performance data continues to be that outcomes collection processes have not been fully adopted or incorporated into study plans.

Securing patient recruitment metrics requires thoughtful preplanning by the study team, ideally as part of a broader strategic metrics plan. Importantly, the metrics plan needs to specify the systems and meth-

ods that will allow tying randomizations back to subject recruitment tactics.

It is also necessary to consider mitigating variables that can compromise the ability to properly evaluate and draw valid comparisons from recruitment metrics.

Factors that need to be accounted for include study design, therapeutic indication, site start-up times, administrative delays, and the enrollment timeline.

### Direct-to-Patient Outreach

Frequently employed direct-to-patient outreach tactics include advertising (print, radio or TV), direct mail or e-mail, Web advertising, pharmacy outreach, and text messaging, all of which lend themselves nicely to metrics collection down to the randomization level.

Deploying a centralized call center and/or Web screener also allows for precise tracking of referrals. Contact centers and Web screeners are accurate vehicles for generating metrics that show which strategies and tactics are effective in producing referrals, pinpointing where specific

strategy modifications may accelerate enrollment. While there have been valiant efforts to capture metrics for calls going directly to study sites, the completeness and accuracy of these data understandably remain a challenge.

While measuring performance outcomes to the point of passing prequalified referrals to study sites is highly valuable in its own right, the holy grail of patient recruitment metrics is the ability to tie tactics to specific participant randomizations, not just the referral of pre-screened potential participants.

It is important to note that successful referral follow-up and management hinges on close collaboration between study sites receiving referrals and the recruitment support team responsible for deploying the patient outreach tactics that are generating those referrals.

### Referral Metrics

Some examples of the granularity with which direct-to-patient outreach results can be captured and evaluated include:

## Summary of Recruitment Measures by Tactic

TACTIC	PERFORMANCE METRICS
On-line promotion of a study Web site with on-line screening	<ul style="list-style-type: none"> <li>• Number of clicks and cost per click</li> <li>• Web screens and cost per screen</li> <li>• Web referrals and cost per referral</li> </ul>
Print/Radio/TV advertising, direct mail, text messaging with centralized contact center screening	<ul style="list-style-type: none"> <li>• Calls and cost per-call</li> <li>• Prescreens and cost per screen</li> <li>• Referrals and cost per referral</li> </ul>
Recruitment specialist site support and materials	<ul style="list-style-type: none"> <li>• Change in screening activity</li> <li>• Change in screen fail rate</li> <li>• Change in enrollment rate (per site or for average of all sites), expressed as a % change from before recruitment support</li> <li>• Time from site activation to first patient screened (assumes support and materials are in place before site activation)</li> </ul>
Referral management	<ul style="list-style-type: none"> <li>• Time from referral to first site contact, on-site screening, randomization</li> </ul>

Source: MMG

**Table 1.** Performance metrics provide a basis of measurement for the effectiveness of both direct and indirect recruitment tactics.

- Number of calls
- Number of initiated and completed phone screenings
- Number of referrals to sites
- Reasons for caller ineligibility
- Number of referrals contacted by site
- Number of referrals who sign an informed consent to screen for the study
- Number of referrals who enroll/randomize into the clinical study

Those metrics can be analyzed using a number of factors, such as outreach method, caller location, and caller demographics. Outreach cost analyses of these metrics can reveal return on investment evaluations, such as cost-per-call and cost-per-referral comparisons.

Conversely, when sites conduct direct-to-patient outreach in a decentralized manner, as when respondents contact sites directly, the ability to track the return on investment for recruitment support is much more difficult and less precise.

### Indirect Recruitment Tactics

Indirect tactics, such as recruitment specialist site support, recruitment materials, and media awareness, are less amenable to concrete forms of measurement. However, they can still be assessed.

It may be impossible to directly tie the provision of clinical study brochures to the enrollment of an individual participant, for example, but it is possible to draw correlations between the introduction of the materials to the site and the site's screening and enrollment activity (patients/site/month) and yield (ratio of enrollments to screenings).

Similarly, the impact of recruitment specialist site support can be compared either to a baseline period before support was provided or to sites that receive no such recruitment support.

Metrics reports for indirect tactics typically include graphs showing changes in the average weekly (or monthly) accrual rates by sites over time and how they correlate to the type of support, whether that be the provision of materials, initiation of recruitment specialist assistance, media

coverage, or community outreach efforts. In cases where the support is provided to a sub-set of sites or in stratified levels, the difference in performance between sites that received support and a comparator group are also charted.

Graphing outcomes in this way can bring a sense of tangible results to the assessment of indirect tactics.

### Benchmarking

Adopting standard recruitment metrics will lay the foundation for developing performance benchmarks for common tactics against which individual efforts can be compared and differences across variables, such as therapeutic area, geographies, demographics, can be detected.

In this way, benchmarking will drive the fine tuning of direct and indirect recruitment tactics, both in regard to when they are used and how they are implemented.

As performance variances for a given tactic become more visible and better understood, the contribution of a patient recruitment provider's skill and ability in tactic implementation (versus selection) will also become more apparent. Therefore, in addition to bringing uniformity to performance analyses, patient recruitment performance benchmarks will ultimately help bridge gaps between expectations and actual performance.

### Summary

Adoption of standardized metrics, rigorous planning to allow the collection and analysis of those metrics, cooperation amongst all stakeholders, and thoughtful evaluation of resulting metrics on each program are needed to make important progress in recruitment performance measurements.

These metrics will ultimately build a body of evidence that can support valuable industry benchmarks and drive strategic improvements in patient recruitment methodologies.

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# Better than a Crystal Ball

Beth D. Harper and Robert Andes

**C**linical research professionals often dream of having a crystal ball that can accurately and precisely predict enrollment performance. Long-used in other industries, modeling and simulation tools represent the future of clinical research planning. They may, in fact, do better than the elusive crystal ball we long for.

Just knowing that a trial will take X months to enroll is one thing. Insight about the drivers of enrollment success and the impact of manipulating various factors is quite another. Here we explore the basics of modeling and simulation and their use and value in aiding enrollment planning and management decisions.

## Modeling and Simulation

Think of operational modeling and simulation tools as a virtual planning sandbox that enables decision makers to practice the performance of their clinical trial. Those exercises take place without exposing real people to real products, without waiting months or even years to see how long it will take to reach target enrollment or how a study might perform. The goal and focus is to understand the impact of different factors on the outcome. For example:

- If we add 10 sites, how much faster could we complete enrollment?
- If we spend \$1 million on a recruitment program, how much faster can we realistically expect to complete enrollment?
- If we add sites in China, what impact will that have on projected enrollment time?

## How it Works

The nuances of technical definitions and differences between modeling and simula-

tion are beyond the scope of this article. It is useful, however, to briefly define some terms and describe some important elements of operational modeling and simulation as they pertain to enrollment planning.

A model is a hypothetical description of a complex process. Simulation enables study decision makers to practice various scenarios in a computer generated model of a clinical trial. Both techniques are typically used when the real process (e.g., conducting a trial) is complex, time-consuming, expensive, and/or dangerous.

For our purposes, models range from simple mathematical equations of a few key metrics to full-blown computerized simulation systems that represent an entire clinical trial process.

Mathematical models (i.e., equations) are created to explain how a certain process (e.g., country allocation or subject recruitment) might work. In computer simulations, professionals build entire processes that reflect real-world activities: the flow of subjects from identification and prescreening through informed consent and randomization, through to trial completion.

## Planning Enrollment

With modeling and simulation, study planners can run multiple trial scenarios, which can reveal missed opportunities or valuable insights. For example, the project team may discover that countries not previously considered could contribute subjects at a lower cost or that a trial could be enrolled in the same time with 45% less sites.

Some industry experts suggest that it costs \$25,000 to \$40,000 to initiate a site; not having to initiate additional sites represents huge cost and time savings. Multiple

## Cycle Time What-if Scenarios



simulation runs may reveal that a trial could take twice as long to enroll as originally planned, which may lead to a decision to cancel the study before it is launched.

**Study Scenario.** Let's say we're planning a large, global Type II diabetes trial of 700 subjects. Very early in study planning we might ask a simple question: Is a six-month enrollment period realistic?

Using past enrollment metrics from a database, some simple modeling could look at various combinations to determine that we could realistically meet the six-month

## Simulations may reveal that a trial could take twice as long to enroll as originally planned.

enrollment goal and that several options exist for the possible mix of countries and sites that would allow us to meet that goal. With little difference in the enrollment and total cycle times, we may choose a scenario with fewer sites and countries to minimize study start-up and monitoring costs.

Multiple stakeholders then weigh in with country recommendations and strategically important factors. The marketing de-

partment has requested including China and enrolling a minimum of 10%, or at least 70 subjects, into the trial.

Although the company has never worked in China, its CRO partner advises them that China's activation process can take about a year. Because a year is an unrealistic time to wait to see whether China can meet the enrollment commitments, the study team does further in-depth modeling and simulation to assess the impact of that wait before making

a final commitment. They learn that adding China will come at a cost of approximately seven additional months from protocol approval to last patient enrolled.

Both the simple quick trial modeling and the country allocation modeling examples use an algorithm with a series of ranking and weighting calculations based on past performance data. The results optimize the mix of countries most likely to meet the enrollment goal of 700 subjects in six months.

China is strategically important, so the study team agrees to include it and revises their enrollment timeline estimate to a more realistic nine months (see Figure 1).

While study implementation activities in the rest of the world proceed, the team now turns its attention to planning U.S. enrollment. They explore options for accelerating enrollment to accrue 300 subjects so that an interim analysis can be completed. The team wants to determine time:cost trade-offs for the following scenarios:

- Invest \$1 million in an advertising campaign expected to accelerate the study enrollment rate in 40 U.S. sites
- Add an additional 10 sites in the United States (a total of 50 U.S. sites)
- A combination of adding 10 more sites and a \$1 million recruitment campaign.

Figure 1 shows estimated enrollment

curves for the three options, and Figure 2 shows a comparison of the time:cost trade-offs for the various scenarios.

What we learned from simulating these scenarios is that we are likely to gain only about one month in cycle time and two weeks additional enrollment by spending more than \$1 million to add more sites and run a recruitment campaign. With that insight, the team may opt to go with their baseline scenario of 40 sites and invest the \$1 million in other improvement initiatives.

### Benefits Realized

The true power and value of operational modeling and simulation decision-aiding tools is the ability to run unlimited what-if scenarios in a matter of minutes.

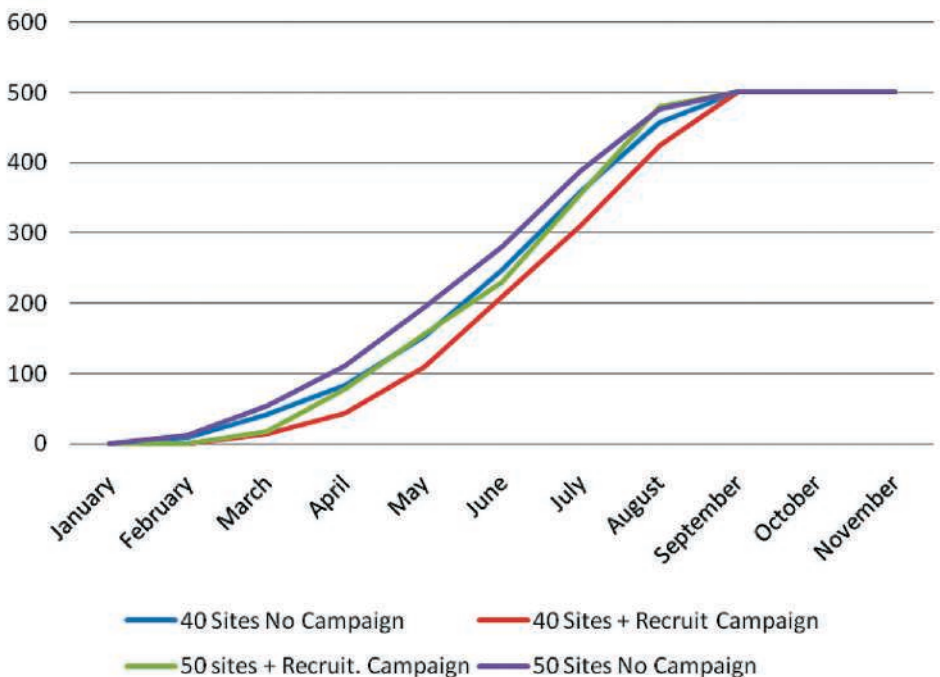
Gaining insight into the likely outcomes may come from various scenarios without actually having to implement those plans, which saves valuable time, money, and re-

## Modeling and simulation tools enable study planners to safely “practice” their trials.

sources. If such decision-aiding tools enable study planners to “practice” their trials in a safe simulated environment—and if practice makes perfect—then modeling and simulation tools give the industry an opportunity to perfect the planning and execution of clinical trials.

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### Simulated Scenario Enrollment Curves



Source: Internal SAI CTInsight Simulation Run Results, Jan. 2009

**Figure 2.** The estimated patient enrollment curves for the four scenarios listed.

Recruitment and retention strategies gain urgency in an era of tighter economic focus.

# The Business of Recruitment

Elizabeth Moench

If ever there was a time for specialty patient recruitment and retention companies to come into their own it is today. Drug development inevitably takes more money and time than companies anticipate.

That means that biopharmaceutical companies often need subsequent rounds of capital investment to raise as much money as possible. Companies must then consider how to manage their money wisely, preserving cash reserves as long as possible and mitigating risk. The latter has critical ramifications.

Companies of all sizes have endless ways to run into problems that cost time and money. Clinical trials, though, fail in one major way: 80% of failures are caused by the inability of research sites to find and enroll sufficient patients and meet timelines. Those trials fail not because of the drug, but because the trial's patient recruitment and retention goals were not achieved.

## Meeting the Challenge

Missed enrollment deadlines lead to an increase in operational burn. A number of biotech and medical device companies have already fallen victim to recruitment problems and tough economic times. For example, Titan Pharmaceuticals, AtheroGenics, Orchestra Therapeutics, and the device company Myocor have gone bankrupt.

Today, more than ever before failure to meet recruitment targets is a barrier that companies must overcome, and they must do so proactively. Otherwise, delays in recruitment and a failure to retain subjects in trials can drain cash reserves needlessly.

Data consistently reveals that recruitment and retention issues have the great-

est impact on clinical trial costs. Furthermore, a recently conducted study asserts that patient recruitment and retention not only affect direct trial costs but also have a huge bottom-line impact when drug trials are delayed. That impact also ultimately affects new product launches as well.<sup>1</sup>

The current drug development environment is made even more challenging by one simple fact: Despite pharmaceutical companies' annual spending of \$60 billion on research, the U.S. Food and Drug Administration is approving a mere trickle of new drugs each year—about 18 to 20 at best. Something has to give.

## Stepping it Up

Economic downturns cause companies to become more efficient and more productive. They analyze where most of their time and money is spent, consider what can be improved, and where they can use more effective processes and management control tools.

For companies involved in drug development, no area is more resource intensive than clinical trials. The subject recruitment and retention environment is changing rapidly. In the new environment, that indispensable activity is being driven by decisions based on return on investment and measurable results.

Clinical trials executives are asking the right business questions about recruitment and retention. They are assessing the value of time saved by implementing a proactive recruitment program, and comparing it to the cost of and recruitment yield from the investment.

All too often failure to reach target dates and numbers can be traced to a

company's complacent watchful waiting approach. Instead, a proactive subject recruitment and retention program designed by recruitment-marketing specialists to support research centers can prevent such problems.

To avoid clinical trial failures, some companies are hedging against the risk of an 80% chance of study delay. They are seeking to change the odds by avoiding a watchful waiting stance, instead proactively investing in a patient recruitment strategy that can minimize risk of enrollment shortfalls and missed deadlines.

Forecasting models now look at the level of recruitment investment and the projected pace of recruitment expected to enroll those who meet inclusion criteria for the trial. They measure those factors against the value of time saved, calculated not only for study cost but also for a broader examination of downstream time and costs saved.

### **Available Help**

Knowing that time is money, several experienced specialty recruitment companies have invested in sophisticated Web-based systems to offer online recruitment and retention management tools. Those tools can expedite the recruitment development process, collect performance metrics in real time, and streamline ongoing recruitment management.

Although a number of marketing and clinical trial management firms have entered the recruitment arena, it is the experienced recruitment specialty companies that developed the first recruitment performance models for benchmarking statistics that can define recruitment forecasts and more accurate trial budgets and timelines.

Setting a concrete strategy based on careful planning and feasibility, sponsor companies can gain much needed control over the entire recruitment process: tracking milestones, assessing return on invest-

ment, and monitoring cash reserves with clear measures of success and failure.

A sponsor's initial focus is always given to recruitment. Nevertheless, there are sound business reasons to proactively implement subject retention programs as well.

A major pharma company recently analyzed its \$2 million, three year investment to retain several thousand patients in its trial. It compared performance metrics and retention rates before and after the program was implemented with other studies involving the same investigational drug and study population. It found that

the program retained close to 700 study subjects who had been at risk of dropping out and resulted in a three

times greater performance rate.

The monetary savings of retaining these clinical study subjects exceeded \$10 million; and that did not take into account the value of stronger clinical data for analysis.

As a head of clinical operations explained, "A retention program is an insurance program. When specific retention targets are set, and retention milestones are achieved, it is easy to measure how much investment for the overall study is preserved."

### **Sites as Businesses**

In today's competitive and economic environments, even clinical trial sites are looking at their practices as businesses. Some are creating a culture of continuous, data-driven, process improvement with a goal of improving overall clinical trial performance and subsequently improving patient recruitment and retention.

For example, forward-thinking study sites recently integrated a case management and patient education approach into the care process for study subjects. Those sites involved in a pre-diabetes study found that this model resulted in a win for all parties: subjects, sites, and sponsors. Compliance improved, sites were more engaged,

**There are sound business reasons to proactively implement subject retention programs as well.**

patient satisfaction was measurable, sites were compensated for continued subject participation, and the sponsor was assured of the statistical power of its data.

Furthermore, sites with a business approach to patient recruitment are focusing on the study subject–time cycle.

For example, sites are assessing how much time it takes to see a new study subject at their first visit. They recognize that they typically spend a great deal more time with the study subject initially than at follow-up visits. They also recognize that the time investment pays off.

### **Those sites willing to invest time and effort into optimizing subject recruitment and retention are those best poised to work with industry long term.**

When business-minded study sites consider the value of the patient after the study is over, they recognize that there is return on investment from study patients and/or the growth of the medical practice.

It takes time to assess new patients for a study. It takes time to answer their questions about it. It takes time to ensure that they understand the protocol requirements. Like the old carpenter's saying "Measure twice, cut once," savvy physician investigators know that their practice can grow through clinical trials, and the thorough assessments they provide.

The assessments and frequent visits can be the first steps in establishing sound relationships. They also help patients—who too often believe that a trial may magically "fix" them overnight—to understand that a quick fix is an unrealistic expectation.

In most cases, what brought them in to a clinical study was the result of years, sometimes decades, of accumulated problems that cannot be solved overnight.

Each trial subject who walks away with a real understanding of what goes into their experimental treatment is more likely to become a long-term patient.

### **In the Final Analysis**

In an environment of cash preservation and a watchful eye on R&D spending, feasibility planning for recruitment that includes market assessments, performance modeling, and the impact of retention is critical. Such modeling helps companies drive their budget decisions, resource allocation, and the assessment of worst- and best-case recruitment scenarios based on recruitment investment and its return.

More than ever before, companies of all sizes weigh considerations of their recruitment investment against the risk of watchful waiting—and doing nothing.

Recruitment modeling must assess operational burn against minimizing the risk of study failure. Whether it is

applying a 10-80 rule (investing 10% of a study's budget to avoid an 80% delay), the bottom line is investing in subject recruitment proactively and wisely. That is the way to achieve return on investment, meeting or exceeding timelines, and preserving cash reserves.

Finally, when sites understand the business value that clinical trials afford them in growing their practice through long-term relationships by offering thorough assessments and frequent patient contact, everyone benefits.

Study sites are starting to see the benefits of defining themselves as centers of excellence. Those willing to invest time and effort into optimizing subject recruitment and retention are those best poised to work with industry long term.

### **Reference**

1. Streamlining Clinical Trials, [www.clinicaltrialbenchmarking.com](http://www.clinicaltrialbenchmarking.com) (2008).

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A predictive enrollment model answers critical questions in subject recruitment planning.

# Removing the Mystique

Jill Pellegrino and Roger Smith

**A**ny sponsor that has approached subject recruitment services with skepticism or trepidation can take comfort in knowing how we transformed over 10 years of patient enrollment data into a highly accurate predictive model.

Our predictive enrollment model answers two critical yet mysterious questions in recruitment planning: How many patients are we expected to get? And by when? The answers enable a trial manager to make a confident investment in recruitment. That is far preferable to the infamous black box “solution” that provides no performance expectations.

## The Calculation

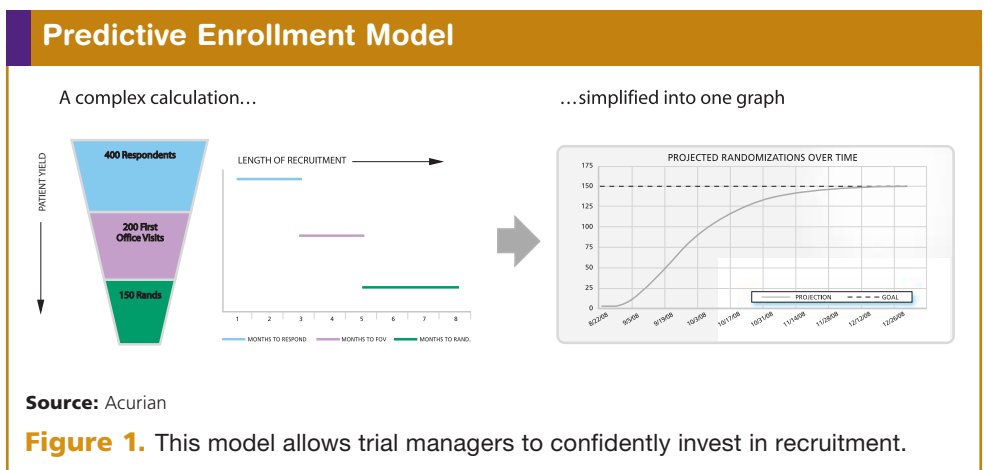
The model is based on calculating the interaction between the two principles central to predicting enrollment: protocol feasibility and recruitment stage timing.

Protocol feasibility is the probability that target patients exist in the addressable population and will agree to comply with clinical

and logistical protocol requirements. This is often expressed by a recruitment funnel. Recruitment stage timing is the average time for patients to complete each milestone in the recruitment process. That is predictable only by compiling an extensive database of recruitment performance history by therapeutic area (see Figure 1).

**Patient yield.** We all know that the number of respondents to a recruitment campaign does not equal the number of people who enroll in the trial. So the model projects the ratio of respondents to enrollees. The recruitment funnel is the input that governs the rate of attrition at every recruitment stage and ultimately determines how many patients enroll.

Estimating the recruitment funnel is difficult because no two trials are the same. A tiny difference between protocol requirements for two trials may cause drastic differences in achievability of recruitment and enrollment timing. This is why every protocol needs to be uniquely assessed. Unfortunately, most people use subjective



## Predicting enrollment timing also enables identification of unforeseen obstacles and challenges early on.

methods to make estimates. Without having a scientific method to estimate patient yield, trial managers resort to anecdotes and guesswork to estimate the recruitment funnel, which rarely works.

Our recruitment performance database of over 1 million patients from actual trials enables an objective estimate of the probability that a patient will enroll.

The database shows exactly what percentage of migraine patients attend their first office visit, and how many Alzheimer's patients respond to a television ad or letter. The database enables the application of known probabilities to a protocol's requirements, defining the funnel with a high level of statistical confidence.

**Recruitment length.** The estimated number of enrolled subjects is only one piece of the puzzle. The other, equally critical, piece is the length of time it will take to recruit the required number of patients. Predicting enrollment timing also enables identification of unforeseen obstacles and

challenges early on. Solving problems early in the recruitment process is the key to successful enrollment completion.

Because timing is such an integral component of a predictive model, it is important to calculate it with confidence. Most recruitment models assume patients enroll in a linear fashion and that an equal number enroll per month. Using the database, which uses actual study data to measure timing behavior, we found that the timing equation does not follow a straight line but the behavior illustrated in Figure 2.

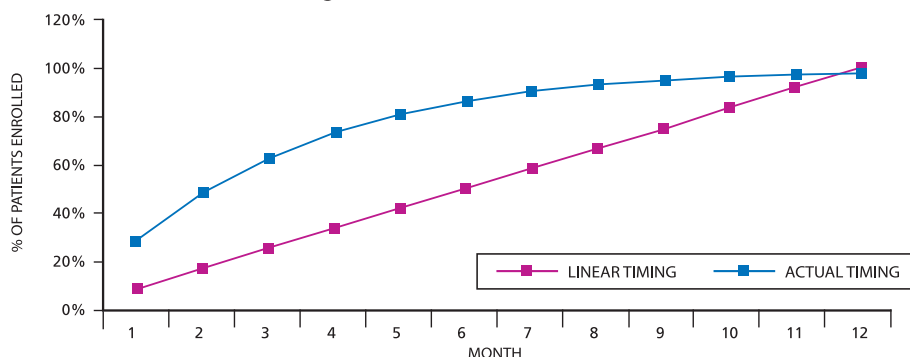
### Expedited Enrollment

Traditional recruitment models use trend analysis to predict enrollment. On day one, a projection is created assuming an equal number of patients enroll each month.

As recruitment progresses, trial managers rely on matching the actual performance to the straight-line projection. When it diverges from that, they adjust the expected line accordingly. Adjusting projected expectations does nothing to help expedite enrollment, for two reasons. First, trend analysis relies on actual performance to make predictions. It takes time, sometimes months, before actual enrollment

## Timing Assumptions

Actual Timing Used in Acurian's Predictive Enrollment Model

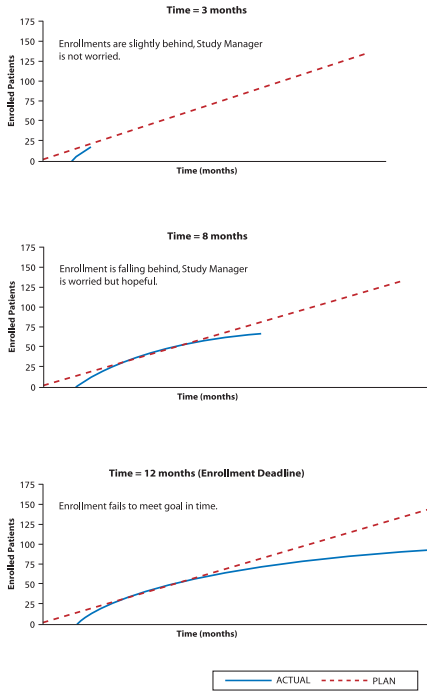


Source: Acurian

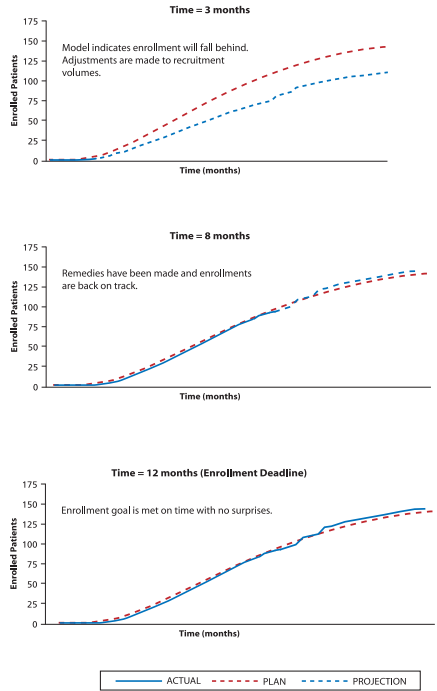
**Figure 2.** The recruitment model, which used data from over 400 actual trials, revealed that patients do not enroll in a linear fashion.

## Comparison of Models Used to Complete Enrollment

### Standard Trend Analysis



### Acurian Enrollment Prediction Model



Source: Acurian

**Figure 3.** A side-by-side comparison of the two different recruitment prediction models over the same 12-month period.

performance is known. By the time the trial accrues enough randomizations to alert managers the plan is behind, it's too late to recover the original enrollment timeline.

Second, trend analysis is backed not by real performance but a flawed timing equation and a gut-based recruitment funnel. So the study team bases its recruitment plan on overly optimistic, impossible, estimations. Furthermore, spotting divergence from a projection provides no new intelligence to help finish successfully.

Contrary to trend analysis that reveals recruitment obstacles after they occur, predictive modeling identifies potential challenges up front, preventing them from transpiring. From the start, there is a realistic plan based on historical performance.

The predictive model projects the number of patients by day through each funnel

stage, not just randomization. This enables identification of harmful deviations that signify enrollment falloff before randomization. With this knowledge, recruitment tactic volumes are predicted to prevent an enrollment slowdown before jeopardizing the enrollment deadline (see Figure 3).

Investing in patient recruitment services does not have to be hit or miss. Predictability is not simply possible, it is measurably valuable to trial managers. When predictions are based on objective therapeutic data, they can enable study managers to design better budgets and build consistently attainable study timelines.

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Solving complex patient recruitment needs by eliminating old habits and moving forward with all encompassing strategic planning.

# Program-Level Branding

Donna Beasley

**M**uch of what we read and what we have heard at every drug-related conference during the past few years proclaims a single prevailing driver for all of today's trends and decision making: tremendous pressure to cut drug development time and costs while at the same time improving safety.

Easier said than done. Clearly, though, innovators are stepping up to the challenge and seeing the results.

## What it Takes

Many times, change is sparked simply by thinking in new ways. Program-level planning for a compound isn't a new thought. What may be new, however, is to consider applying that level of planning to more specific tasks associated with each protocol's completion. That is what some sponsors are doing in the patient recruitment arena with measurable success.

Strategic program-level subject recruitment planning is about taking your clinical program for a particular compound and planning for enrollment of its clinical trials as an entire program rather than on a protocol-by-protocol basis.

The most common strategic planning mistake for recruitment is the lack thereof. Often, there is no planning for recruitment at all. No drug will ever make it to market for any indication unless patients enroll in the trials to test the compound. Patients are one thing we cannot succeed without.

Now consider that nearly 90% of clinical trials are delayed by slow patient enrollment. That's when it begins to make sense to think that a focused investment in a strategic program-level subject re-

ruitment plan will result in reduced drug development time and costs and achieve the improved safety goal.

Program-level recruitment strategy is about working smarter, not harder. It's about considering the patient or target audience from day one and crafting a global plan for enrolling patients across the entire program of studies. It's about being proactive and using metrics to drive the recruitment strategy as well as intelligent design to mold it all along the way.

And these types of programs give sponsors a number of advantages.

## Maximizing Awareness

Program level recruitment planning allows sponsors to maximize awareness of their studies. This means more potential study subjects will inquire about participating, resulting in quicker enrollment. Sponsors experience integrated enrollment.

Real strategic planning for the whole program allows sponsors to seamlessly maximize the resulting inquiries from every individual to expedite subject enrollment across the program. That's a significant improvement over wondering about each individual site's and/or protocol's enrollment as it comes up.

Efficiencies will be realized in a number of areas. These include contract negotiations, media buying, and communications planning, as well as in nearly every measure of study success.

Sponsors also reduce costs through early study enrollment, negotiating lower rates because of multistudy discounts, advanced commitment savings, and the need for less frequency of the study enrollment message.

Intelligent design results from program-level recruitment. Because all enrollment results are collected in one place program-wide, metrics are analyzed in a relational perspective in real-time to identify modification needs for the current program.

These adjustments can then be made very quickly. The results can also be used to project both future study enrollment strategies and needs.

The key to success here is having done the proper level of planning in the early stages and setting in place a solid foundation from which to work. Having a strong metrics driven strategy and powerful creative development in place creates a study environment healthy for positive ebb and flow toward the ultimate end goal of faster, safer and less expensive trial completion.

### Advantages Demonstrated

These advantages are best demonstrated in two sponsor examples. One sponsor's protocols were sequential, while the other sponsor's was simultaneous.

**Sponsor A.** This first sponsor faced a difficult scenario, in which protocols ran sequentially. The baseline setup: The sponsor is entering Phase II studies of a compound, having great difficulty with enrollment early on, and knowing they had a long way to go. Once the sponsor realized the challenges ahead, they sought out assistance in developing a recruitment program strategy. Their program was designed in every aspect with the target audience in mind, from brand identity to messaging to delivery.

When the recruitment program for the first protocol launched, it enrolled patients in 76 sites and shaved off 13 months from the projected enrollment time.

The second protocol's patient recruitment program launched in 50 sites, with 50% of those repeat markets from the first protocol. Building on the awareness

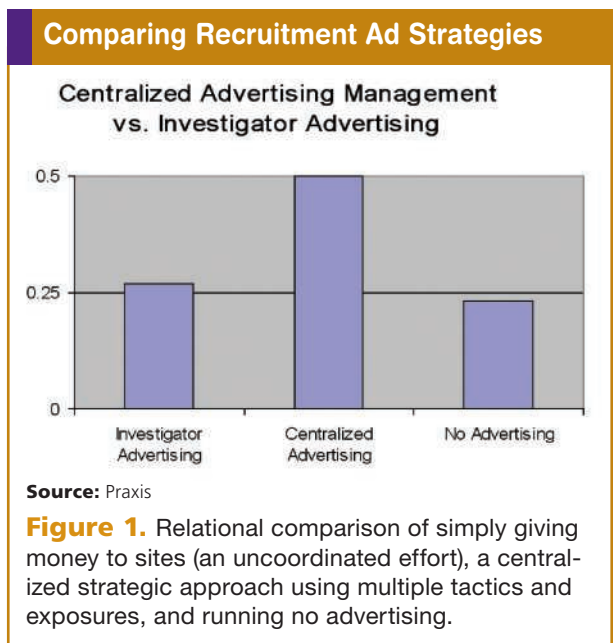
**Through a centralized strategy, all interested candidates were evaluated for their qualification for any protocol in the program.**

created during the first protocol's recruitment campaign, the screening rate for the second protocol increased 22% over the first, and the study enrolled 10 months ahead of plan.

An international study is now underway, and planning for the next round of 2010 enrollment launches has been established using the campaign extension of the now-established brand.

Domestically and globally at the sites and corporate-wide, the program is collectively known and referenced by the recruitment campaign brand name.

Ultimately the success of this program was driven by early stage accurate identification of the target audience most likely to be interested in and qualify for the trial as well as creating a strong brand identity



that the same audience would not only recognize over time but also closely identify with, from one study to the next and into the future.

**Sponsor B.** The second sponsor was enrolling three Phase III protocols simultaneously. The protocols were similar in na-

ture, yet specific criteria for each excluded some potential patients from one study, while at the same time qualifying the same patient for inclusion in another.

Using centralized recruitment tactics on a market-by-market basis, all sites located within a given area received prequalified candidates for the protocol they were participating in.

This was accomplished for just one-third the media and management costs that would have been expended had the three study protocols been managed in an individual, non-centralized manner or if the sites had been responsible for recruiting on their own (see Figure 1).

### The key to success was looking at one comprehensive challenge rather than each protocol.

The sponsor needed a combined total of over 3500 randomized patients. With over 200 sites participating, there was a lot of market overlap in terms of site location.

The key to success was looking at the entire program from the perspective of one comprehensive challenge rather than looking at each individual protocol as a separate goal to be reached.

Through a centralized strategy under a single comprehensive recruitment campaign, all interested candidates who inquired about the study were evaluated

### Planning for Success

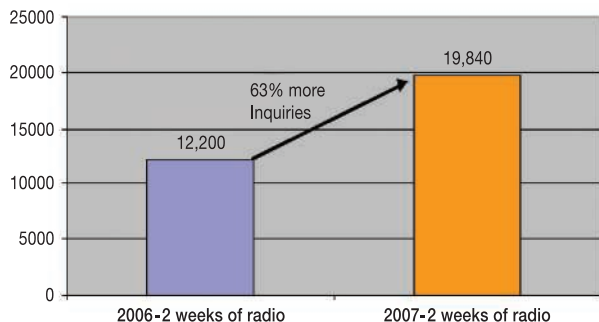
In situations such as these, broader level planning becomes a necessity for success. This allows for the recognition of pending challenges with site database exhaustion, the need for outside assistance, and the importance of multiple exposures to the study message across varying tactical executions (see Figure 2).

Building a program-wide campaign based on metrics, and managing it through intelligent design, resulted in a program that helped the sponsor reach its enrollment goals in order of priority.

Implementing strategic program-level recruitment plans enroll studies more quickly at less cost. It's an all encompassing approach that forces strategic planning and maintaining focus on reaching that all important long-term goal of getting new and better products to market faster and safer than ever before.

**Donna Beasley** is vice president of operations and marketing with Praxis Communications, Brentwood, TN, [www.GoPraxis.com](http://www.GoPraxis.com).

### Multiple vs Stand-Alone Exposure Tactics



Source: Praxis

**Figure 2.** The compounding effects of multiple messages were revealed by a case study of a two-week radio flight run as a stand-alone tactic in 2006 versus a two-week radio flight run in conjunction with other targeted tactics in 2007.

Using a Web site strategy to develop and implement a worldwide recruitment program.

# Global Subject Recruitment

Melynda Geurts and Lacey Blowers

**G**lobal patient recruitment today requires a multilayered, multifaceted approach to bring to fruition the most effective outcomes within predicted recruitment timelines. This approach requires constant monitoring and updating of regulatory implications, customs, and guidelines in all areas of practice.

Here we specifically focus on the many challenges and opportunities presented when using study-specific Web sites as a global recruitment strategy.

Study-specific subject recruitment sites are growing in popularity, with 68,458 clinical trials listed with the National Institutes of Health (NIH) in 2009. The PEW Internet Health Study<sup>1</sup> reports the following:

- Eight in 10 Internet users go online for health information
- 113 million consumers have searched for health and wellness information
- 73% of chronic disease sufferers searched the Internet on their disease
- 75% found information that affected their decisions related to treatment
- 69% asked their physician questions and/or sought a second opinion

This heavy reliance on the Internet mirrors the boom in Web browsing for health information globally. With increasing Internet penetration, online recruitment offers broad geographical reach, an educational platform for patients, and cost savings over more expensive forms of advertising.

## Web Strategy Challenges

Web initiatives are fairly straightforward in the US, primarily due to the fact that most sponsors' privacy policies and regulatory guidelines cover users based in the US.

In contrast, as an international strategy, using the Web can prove to be more time consuming and costly because of the shift in the audience.

For example, in a recent project where 10 countries were proposed for Web initiatives, only two countries were mobilized. Countries initially proposed included India, the United Kingdom, Spain, France, Germany, the United States, Mexico, Switzerland, and Belgium. Only the programs in India and the United States received approvals within reasonable timelines.

Other significant challenges for a Web-based strategy may include:

- Version control
- Cost implications
- Privacy policies
- Ethics committee rulings
- Timelines
- Challenges related to patient screening tools on the Web site

## Web-Based Recruitment

Based on the complexity of planning for Web development, our company and its clients have embarked on extensive country-by-country research into Web-based practices. This data is reported through interviews and actual regulatory or Web-based documentation.

The following are examples of the type of data collected to help support Web-based strategy and to document regulatory guidelines.

**Mexico.** Establishing a Web site for a clinical trial does not seem to be prohibited, but probably would be ineffective, says Gina Gorodezky, MD, Medical Director of IMIC, a Mexico-based CRO. "The Mexican population that participates in

## Multinational Web Plan

SPANISH		COMMENTS
Sites	11	<p><b>Guatemala.</b> Sites very interested in using the Web site to promote the trial according to CRA information. Availability of the Internet is greater than in Mexico. Web site content will be available in Spanish and should be submitted to Guatemalan EC.</p> <p><b>Spain.</b> The Royal Decree, most recently updated on March 3, 2008, neither specifically permits nor prohibits using a Web site for patient recruitment purposes. Spain has adopted the EU Clinical Trials Directive, which allows for patient recruitment methods. Spain EC (Centro Coordinador de Comités Éticos de Investigación Clínica) permits patient-targeted Web sites, which must be approved.</p> <p><b>Mexico.</b> GCP guidelines allow advertising for subjects, but have no mention of such methods as radio, TV or the Internet. Considering the use and availability of the Internet, this country is not recommended for use of the Web site.</p>
Cost	\$2,283	
Translation Due Date	TBD	
Live Date	TBD	
GERMAN		COMMENTS
Sites	29	<p><b>Germany.</b> No legal obstacle to patient recruitment through Web sites, which have been successfully used for many trials in Germany. ECs must approve the text and content.</p> <p><b>Austria.</b> Radio, newspaper, flyers, and Internet advertising are all possible. Ethics committee must review and approve all of the text. Web sites have previously been approved as a recruitment strategy for clinical trials.</p> <p><b>Switzerland.</b> The regulations make no mention of using Web sites to create awareness of a clinical trial or to screen potential subjects. It is worth noting that Switzerland is not a member of the European Union, so it does not operate under the EU Clinical Trials Directive. Considering stringent requirements detailing where the information is sent and the measures in place to prevent a Web site from targeting patients who may already be participating in another clinical trial, submission for Switzerland is not recommended.</p>
Cost	\$2,395	
Translation Due Date	TBD	
Live Date	TBD	
FRENCH		COMMENTS
Sites	21	<p><b>France.</b> ECs grant final approval of Web sites. The French Regulatory Agency (AFSSAPS) permits the use of Web sites for patient recruitment. Web sites cannot mention the product name, commercial name, logo or branding. Information permitted: the disease, the description of the clinical trial, the mechanism of action of the drug(s) tested, and the sponsor name. Those promoting the Web site in French-speaking countries will provide a URL that directs the user to the French version, rather than linking to the French version through the home page.</p> <p><b>Canada.</b> Many trials in Canada have successfully used Web sites to recruit subjects. English and French will be promoted.</p> <p><b>Belgium.</b> Belgium supports the EU Clinical Trials Directive and has one of the most efficient approval processes. The Internet is widely used, and sites are interested in using the Web to recruit patients. The concern in Belgium is the lack of a Flemish translation, which is why no submission of the Web site to the EC is recommended for this country.</p>
Cost	\$2,395	
Translation Due Date	TBD	
Live Date	TBD	

Source: D. Anderson & Company, 2008

Table 1. A Web-based recruitment plan for implementing a global Web strategy.

clinical trials does not have access to a computer,” Dr. Gorodezky says. She adds that screening of potential subjects is to be done in person.

Sergio Guerrero, MD, Vice President and Chief Operating officer of INC Research offers a slightly different opinion. He agrees that few prospective subjects would have access to a computer but comments, “This might change over time, once middle and high socioeconomic patient populations start participating in clinical trials. For now, it is limited.”

**India.** Estimates of Internet use in India vary from 21.1 million users—a mere 2% of the population—to 37 million, representing 3.7% of the population. Clearly, Internet use and availability is severely limited in India, although it is expected to grow.

While the regulations do not specifically mention the use of Web recruitment methods, the Indian Council of Medical Research (ICMR) posts on its site<sup>2</sup> a “Model form to be filled by the Principal Investigator (PI) for submission to Institutional Ethics Committee (IEC).”

In item 9, the PI is asked: “Will any advertising be done for recruitment of Subjects? (posters, flyers, brochure, Web sites—if so, kindly attach a copy).”

Regarding the likelihood of using recruitment Web sites, Pamrod Julka, MD, a professor of oncology at All India Institute of Medical Sciences in New Delhi, states, “The regulations do not disallow Web sites. However, this method may not be an effective patient recruitment tool simply due to the nonavailability of the Internet to a large proportion of people and illiteracy.”

**Austria.** ClinLife Austria is a registry of clinical trials (<http://www.clinlife.at/>) taking place in that country. Potential subjects can submit contact information after identifying studies of interest. That information is forwarded to appropriate investigative sites. It appears that the sites then contact the individuals and prescreen them over the telephone. An English transla-

tion of this service appears at <http://www.clinlife.co.uk/participating/how>, which is the UK version of this service.

In outlining the conditions for enrolling a compromised patient into a clinical trial, the Medical Devices Act mentions the posting of that trial on the hospital’s Web site. Therefore, posting of clinical trials on Web sites is clearly possible.

## Global Case Study

Table 1 on the previous page describes a multinational, Web-based recruitment plan. It includes actual research and translation costs for the countries mentioned.

This is meant to illustrate the level of detail, planning, and complexity involved in implementing a global Web strategy.

## An Important Tool

We have briefly illustrated the importance of Web sites as a recruitment tool and highlighted the level of complexity

## Successful global recruitment campaigns are possible, but they require research, planning, and keen analysis of cost/benefit ratios.

and the expertise required to implement Web recruitment on a global basis.

Successful global campaigns are possible, but success requires research, planning, and keen analysis of cost/benefit ratios.

Maintaining a realistic perspective and understanding the complexities of the process will help recruitment teams realize the many advantages of Internet-based patient recruitment initiatives.

## References

1. The PEW Internet Health Study, October 2006-2007.
2. [http://icmr.nic.in/human\\_ethics.htm](http://icmr.nic.in/human_ethics.htm).

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