

10 Steps to Faster Enrollment:

Optimizing Patient Enrollment in Clinical Studies

WHITE PAPER

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Introduction

Enrollment is the single factor that most centrally determines the cost and duration of a clinical study. According to CenterWatch, studies enroll on schedule only 10% of the time in the US.¹ While offshore studies do better, the situation remains dismal: 14-17% on time.²

Patient recruitment accounts for as much as 40 percent of the cost of a clinical study.³ The direct costs of patient recruitment can indeed be high, but they are dwarfed by the indirect costs. In addition to study costs, the cost of sustaining even a small company—its “burn rate”—can easily be \$1 M a month. Delays are costly whether a product fails or succeeds. If a product fails, a delay can cost the sponsor a great deal of capital. If a product succeeds, even a day’s delay in availability costs the sponsor dearly, with niche drugs losing about \$1 M of revenue-per-day and blockbusters close to \$5 M.⁴

Enrollment is often delayed for a simple reason: the inability to effectively manage. What hinders management is a lack of information needed to manage any complex undertaking—information allowing the manager to determine where to make changes in order to get better results. When enrollment is going poorly, study managers seldom know why. The study team exhorts sites to do better but lacks the information needed to tell the sites how.

Current “best practices” in patient recruitment still lead to poor results for want of information. These so-called best practices help identify sources of patients based on epidemiology, experience and specialized databases. Beyond that, however, these best practices are surprisingly passive and static.

Drug and medical device developers need to assume current best practices as a starting point, but enroll patients much more efficiently by using an active, dynamic approach to manage everything that happens after site selection. Technology and processes should track enrollment progress in detail, identifying the strategies and tactics that are actually working in the field, and optimizing continuously based on what is learned.

1 Centerwatch Surveys of U.S. (2009, n=950) investigative sites.

2 Centerwatch Surveys of Asian (2006, n=156), Latin American (2005, n=317), and European and Canadian (2006, n=356) investigative sites.

3 Combating the R&D Productivity Decline: Can Big Pharma Reverse the Trend. Report from the Scrip R&D Productivity Summit, London. Genetic Engineering & Biotechnology News. Vol. 26, No. 13. July 1, 2006.

Available from: <http://www.genengnews.com/gen-articles/combating-the-r-d-productivity-decline/1819/>

4 Cruz Rowe J, Elling M, Hazlewood J, Zakhary R. A cure for clinical trials. The McKinsey Quarterly 2002 No. 2. Available from: <http://www.caplax.com/pdf/Clinical%20Trials.pdf>

10 Steps to Faster Enrollment

1. Refuse to Accept Poor Enrollment

Despite pervasive and serious enrollment issues, far better enrollment performance is possible. Based on experience successfully enrolling studies in a variety of therapeutic areas and geographic regions, the normal rate of enrolling on time should be closer to 80% than the prevailing 10 percent. Sponsors who accept poor enrollment performance will get exactly that. The first step to greater success rates in enrollment is breaking with the dismal past and realizing that better performance is possible.

2. Cast a Global Net

An article in The New York Times shows the need to think of recruitment in global terms.⁵ Often patients in the U.S., even in the face of severe risks, are unwilling to consider an alternative to the current standard of care. In regions where fewer treatments are available and the standard of care is lower, many patients find a promising new treatment their best option. Such patients must, of course, receive thorough, accurate information about the risks associated with a new treatment.

Costs and the availability of both investigators and patients are driving rapid globalization in clinical research. The number of active investigators outside the U.S. is growing, especially in China (24% annual growth rate 1999-2004), India (18%), Central and East Europe (15%), and Latin America (11%).⁶

Case Study: Global Enrollment for a Multiple Sclerosis Study

In seeking global sites, the CRO considered sites throughout the world, including Latin and Central America, China, and India. After detailed feasibility work, the sponsor decided to rely primarily on sites in Eastern Europe because of excellent patient supply and the best balance between Western orientation, experience, and demonstrated quality. As part of this planning, two tiers of backup sites were also identified. The first tier was in countries already included in the study, allowing quick startup because of prior regulatory approval. The second tier of sites was in Russia, which offered more potential sites but longer startup times. As part of contingency planning, detailed tracking metrics were established and automated notifications incorporated in the electronic data collection systems. The study is currently in progress, but the ex-US sites are enrolling at a rate several times that of the US sites.

5 Kolata G. Lack of study volunteers hobbles cancer fight. The New York Times. August 2, 2009.

6 Tufts Center for the Study of Drug Development 2006, from IMS and FDA 2005 data

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Conducting clinical studies in China is far less expensive than in the U.S., although estimates of savings vary greatly.^{7,8} Estimates indicate total drug development costs in India are 30 to 50% lower than costs for comparable studies in the U.S.⁹ A recent survey indicates that one third of phase III studies sponsored by the 20 largest U.S.-based pharmaceutical companies are conducted outside the U.S. Most of the sites in those phase III studies are also outside the U.S.¹⁰ Using offshore sites has accelerated enrollment for many studies.

Caution: Global Studies Strain Management Capabilities

The success of global studies depends on the ability to track site performance and enrollment progress continuously and to intervene rapidly regardless of where sites are located. Global studies require an extremely efficient, data-driven management approach.

3. Manage Enrollment

In order to improve enrollment performance, sponsors should implement a dynamic process that optimizes results through active management based on a continuous, detailed stream of real-time information about enrollment progress. This approach differs from best practices, which are helpful in planning a study but do not allow timely mid-course adjustments during the study. Study managers need ready access to the data needed for changes to the strategy and tactics, and the continued ability to closely track and rapidly assess the effects of every intervention. Tracking and adapting must take place both at the site level and study-wide.

Study managers can improve enrollment performance by using metrics to analyze the effects of different practices, promotional messages, media and techniques, as well as the occurrence of specific inclusion/exclusion criteria and causes of screen failure. Management of the enrollment process includes definition of the protocol and selection of investigative sites, but begins in earnest when sites start attempting to enroll patients. Rather than awaiting periodic enrollment figures, study managers must continuously observe and adapt as soon as tracking data indicates the need for a change. Detailed tracking information allows managers to adjust strategies and tactics continuously and allocate resources to the most productive approaches. This maximizes the number of patients through the door, minimizes the number of screen failures and ensures high continuation rates. The result: more studies enroll on time.

7 Reymond E. China lives up to outsourcing hype. Outsourcing-pharma.com. 2007 Jan 16.
Available from: <http://www.outsourcing-pharma.com/Clinical-Development/China-lives-up-to-outsourcing-hype>

8 Behera D, Shindikar A. Clinical trials: Growing opportunities for India. Pharmainfo.net.
Available from: <http://www.pharmainfo.net/reviews/clinical-trials-growing-opportunities-india>

9 Rahul Das D, Sharma A. Destination: India. Drug Discovery & Development. 2007 Aug 1.
Available from: <http://www.dddmag.com/destination-india.aspx>

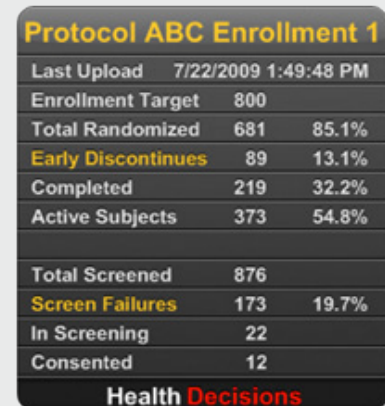
10 Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. N Engl J Med. 2009;360:816-23.

Using these best practices, as well as efficient site closeout driven by performance metrics, allowed an Alzheimer's study to save 1.6 years and \$32 million in direct costs against the sponsor's original projections of five years and \$110 million.¹¹ Sometimes the primary enrollment challenge comes in the form of extremely short timelines with a hard end date. That was the case with a phase II study of a universal flu vaccine discussed below.

Case Study: Completing Enrollment Before an Early, Hard Deadline

A phase II study of a universal flu vaccine candidate faced a challenging, rigid enrollment deadline and yet managed to meet targets within the required time frame. The study did not begin until the start of April, but had to complete both enrollment and dosing by the end of June. There was no flexibility about the deadline for completing enrollment and dosing because the study's comparator was the previous year's standard flu vaccine. That vaccine expired on June 30.

If the study failed to enroll and treat the target population of 80 subjects by that date, the results would be invalid. The study relied on both web-based enrollment reports and desktop reports. The desktop reports, like the one shown here, automatically updated within minutes of the sites inputting patient data, and were crucial to meeting the accelerated timelines.



Protocol ABC Enrollment 1		
Last Upload	7/22/2009 1:49:48 PM	
Enrollment Target	800	
Total Randomized	681	85.1%
Early Discontinues	89	13.1%
Completed	219	32.2%
Active Subjects	373	54.8%
Total Screened	876	
Screen Failures	173	19.7%
In Screening	22	
Consented	12	
Health Decisions		

4. Demand Timely, Meaningful Enrollment Data

Study managers must insist on the availability of real-time data that enables timely adjustments to an enrollment strategy. Otherwise, managers must either accept a passive role and await developments, or try to manage based on missing or incomplete information, risking costly errors. When the right information reaches the right eyes at the right time, everything changes. The standard for judging the timeliness of enrollment data is time to actionable information, which should be within minutes of sites inputting data.

Meaningful Metrics

Even the best planning efforts based on the best available data may fail to predict the tradeoffs of specific inclusion/exclusion and withdrawal criteria in a specific study. These effects must be understood from closely tracked, detailed study data and performance metrics. The sidebar on the next page provides a selection of frequently used metrics.

¹¹ Schoenberger C. An Alzheimer's drug goes on trial. Forbes Magazine, March 20, 2000, pp. 94 - 6.

5. Use the Right Technology Platform

Reliably securing timely, meaningful data on enrollment and other key study operations requires efficient infrastructure. Both data capture technology and site management software play important roles in ensuring the continuous flow of timely information about site performance. For example, without early information about the reasons for screen failures, it is impossible to know whether inclusion/exclusion criteria have already precluded reaching enrollment targets. With such early information, modest adjustments to inclusion/exclusion criteria often substantially speed enrollment.

Data Capture

No data capture technology will substantially increase efficiency unless 1) site personnel record, transcribe and enter data and 2) the systems quickly transform raw data into useful, actionable information. If site personnel leave data on charts for weeks before transcribing it and keying in the data, information becomes available too late for study personnel to efficiently manage. As a result, ease-of-use and convenience for site personnel become major considerations in selecting a data capture system. Unless the system has integrated processes that generate advanced reporting, the success of the study is at risk. Most webEDC systems concentrate on patient data almost to the exclusion of other performance metrics. Numerous other usability aspects of common EDC systems frustrate sites and limit their ability to conduct studies efficiently.¹² It is only human to postpone tasks that combine tedious manual labor and software inconsistent from one sponsor and study to the next.

Some advanced data capture systems do address ease-of-use issues and rapidly transform raw data into useful information. One such system captures data with a digital pen, providing a convenient and intuitive means of data entry. Independent comparative studies of data capture methods in clinical trials confirm the digital pen's accuracy, speed, ease of use and resulting benefits.^{13,14} Site personnel can easily carry the pen from one examination room to another instead of lugging a laptop computer around—which can be awkward for both patients and site personnel.

Enrollment Metrics

1. Patients screened
 - Number
 - Referral source
2. Time from referral to initial screening
3. Patients enrolled
 - Number
 - Percent of target achieved
4. Number active at each stage
5. Number completing each study visit or milestone
6. Frequency and reason for screen failures
7. Number, reason and timing of patient dropout and loss to follow-up
8. Projected dates for Last Patient In and Last Patient Out
9. Screening-to-Enrollment intervals

Adapted from Rosenberg, The Agile Approach to Adaptive Research: Optimizing Efficiency in Clinical Development

12 Borfitt D. Investigative sites: the trouble with e-clinical technologies. eCliniqua. June 1, 2009.

13 Estellat C, Tubach F, Costa Y, Hoffmann I, Mantz J, Ravaud P. Data capture by SamrtPen™ in clinical trials: A qualitative and quantitative study. *Contemp Clin Trials*. 2008; 29:314-23.

14 Cole E, Pisano ED, Clary GJ, Zeng D, Koomen M, Kuzmiak CM, Seo BK, Lee Y, Pavic D. A comparative study of mobile electronic data entry systems for clinical trials data collection. *Int J Med Inform* 2006; 75:722-9.

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Uploading data is a simple matter of docking the digital pen in a device connected to a PC. Within minutes of docking the pen, the data is passed on to study managers enabling more efficient enrollment management. The subsequent information flow, analysis, reporting and management processes are more important than the data-capture technology viewed in isolation. All of these elements contributed to the success of enrollment in a recent study of a molecular diagnostic product.

Case Study: Rapidly Excluding Patients Who Fail to Meet Enrollment Criteria

The company developing a molecular diagnostic product for the HPV market needed to assess the device by testing women with abnormal PAP smears, about 5-8% of women screened. Because of challenges with data systems, the original plan was to enroll all women who received PAP smears at the participating institutions, regardless of the result, even recognizing that only the small portion with abnormal results would contribute useful information. The CRO recognized that the efficiency and timelines of the study depended on immediate flow of PAP results and rapid determination of patients with normal results in order to exclude them from the study. The SmartPen, a digital pen-based system, provided immediate site data that was integrated with laboratory results to ensure enrollment of only those women with abnormal PAPs. Remarkably, a large multinational company developing a competing product faced the same challenges and was unable to implement an efficient, rapid procedure for excluding patients with normal PAP smears. As a result, the study of the multinational's product enrolled almost ten times as many women. The device developer tested far fewer patients and spent much less money, but reached market more than two years before its competitor.

6. Know Where to Focus Your Recruitment Efforts

Surprisingly, nearly all studies start with a recruitment strategy that survives more or less intact throughout the study, even in the face of poor enrollment. By contrast, successful programs try a variety of strategies, tracking the success of different messages, media usage and distribution methods.

It is becoming increasingly more feasible to systematically analyze not only the absolute effectiveness of different recruitment strategies, but their cost-effectiveness as well. For example, in a study of irritable bowel syndrome, researchers developed an Efficacy Index (EI) to compare recruitment methods.¹⁵ The researchers compared such methods as physician referral, newspaper advertisements, fliers, radio and television commercials, internet ads, mass-transit ads, and even ads in movie theaters. The researchers found that the cost for generating a call from potential subjects ranged from \$3 to \$103, and the cost for actually enrolling a subject ranged from \$12 to \$584. In a 1000-patient phase III study, the sponsor could have spent \$584,000 without suspecting that \$12,000 would have

15 Feman SPC, Nguyen LT, Quilty MT, Kerr CE, Nam BH, Conboy LA, Singer JP, Min Park M, Lembo A, Kaptchuk TJ, Davis RB. Effectiveness of Recruitment in Clinical Trials: An Analysis of Methods Used in a Trial for Irritable Bowel Syndrome Patients. *Contemporary Clinical Trials* 2008 Mar;29(2):241-51.

achieved the same result. Such enormous differences show why enrolling efficiently requires a continuous flow of such detailed information on the effectiveness of different strategies and practices.

7. Make Contingency Plans

When it becomes clear that a study needs to add investigative sites, a quick response is essential. Studies can't wait until timelines are in jeopardy to identify expansion sites. Study managers should not only identify a second tier of appropriate sites from the outset, but also make preparations for activating the sites quickly. This requires completing all long-lead-time activities required to activate the second tier of sites well in advance. Such activities include ensuring that regulatory requirements are met. Managers of one large breast cancer study incorporated a tiered enrollment strategy, made all necessary preparations to act if enrollment lagged, and acted swiftly when data indicated it was necessary.

Case Study: Contingency Plan to Expand Cancer Study Offshore

Although the sponsor preferred to use only U.S. sites, the CRO considered the risk of enrollment delays high. The CRO's study managers incorporated a contingency plan that would add sites in Russia and other countries with minimal delay if U.S. enrollment fell short of goals. When the study began, enrollment metrics showed U.S. sites enrolling at less than one patient per site, per month. The study quickly added 27 sites in six countries. Managing these sites with the aid of daily enrollment metrics allowed recruiting 282 patients in nine months, a new record for published mBrCa studies.

Another contingency plan for accelerating enrollment focuses on expanding enrollment at the existing, most successful sites rather than adding more sites. That strategy enabled a study for a drug used to treat cocaine-dependence to complete enrollment two months ahead of schedule.

Case Study: Contingency Plan for Rapid Expansion of Enrollment at the Most Successful Sites in a Phase II Cocaine-Dependence Study

In this study, the CRO identified the best-enrolling sites and asked if they could enroll more patients with increased resources for staffing and advertising. Several sites agreed. The CRO amended contracts and funneled increased funding to these sites. Some sites assigned routine administrative tasks to staff members added at this time and assigned recruitment responsibilities and an increased patient load to more experienced staff. The CRO provided web-based training for new site employees. The study completed enrollment, two months ahead of the target date.

8. Share Best and Worst Site Practices

Sometimes close tracking of site performance metrics pays off with early discovery of one site that is far outperforming all others. Personnel at this site may have a deeper understanding of the patient population and its behaviors, resulting in a novel enrollment strategy. Study managers may wonder why they didn't come up with this strategy, or they may realize that it would not have occurred to them if they conducted a thousand similar studies. The latter was the case with one study of a treatment for a sexually transmitted disease (STD).

Case Study: Identifying and Sharing Best Practices in an STD Study

In a study of a treatment for a sexually transmitted disease, close tracking showed that all six sites were enrolling patients at similar rates, averaging 3.1 patients per month. This was well below the target rate of five patients per site per month. However, it soon became apparent that one site had suddenly begun to enroll patients at almost twice the initial rate. Real-time enrollment metrics illustrated this change and monitors called the site to learn why. Surprisingly, the site had increased enrollment by posting flyers in nightclub restrooms. The study manager encouraged other sites to follow suit and provided supporting materials and funds for printing and distributing the flyers. Enrollment increased to an average of 8.1 patients per site per month (Figure 1). The study met its goal of enrolling 330 patients two months ahead of schedule.

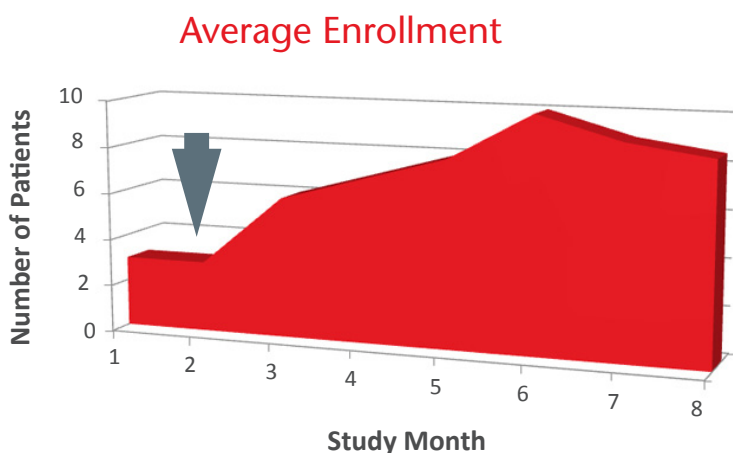


Figure 1. After sites in an STD study began advertising in nightclub restrooms.

As shown in this example, sponsors can accelerate enrollment by collecting promotional materials used successfully at one site and share these study-wide through a study website. Sites can leverage the work already done by their peers rather than try to address every recruitment need independently.

9. Don't Multiply Inefficiencies When Adding Sites

Adding sites is often the right solution to slow enrollment, but many sponsors postpone this step due to associated costs. Sponsors rightly sense that adding sites may not merely increase costs, but send costs spiraling out of control. This fear is well-founded. Adding sites can multiply any inefficiencies in site management, monitoring and a host of other site-related activities. The marginal cost of adding sites—including costs not directly associated with enrollment—becomes a major issue.

However, there are indicators that sponsors can use to determine whether the study has inefficiencies that will get worse with the activation of each new site:

1. How quickly the CRO realizes that enrollment is in trouble
2. How much detailed information the CRO provides about the enrollment issues causing delays
3. How much the CRO leverages technology in study operations

If a CRO informs your sponsor early of the need for additional sites and uses detailed tracking information to explain the issues, the CRO will be able to minimize the costs of additional sites through tight management based on detailed, timely information. If a CRO presents your sponsor with an enrollment crisis at a distressingly late date and only knows that there aren't enough patients, the CRO won't know enough about what's happening at additional sites to control costs—or to speed up enrollment. As studies grow, it becomes more important than ever that CROs use an efficient metrics-driven approach to manage enrollment, and to manage other study operations as well.

Sponsors should give monitoring methods particularly close scrutiny before adding a second tier of sites. When a study adds sites and CROs use outdated monitoring methods that pile up high travel expenses for exorbitant numbers of on-site visits, monitoring costs soar. Suppose a study starts with six sites and adds six more. If each site requires a dozen on-site visits, the sponsor pays for 144 trips. But if the CRO uses remote monitoring plus four on-site visits to each site, adding six sites requires the sponsor to pay for only 48 trips. Adding six sites with the old-fashioned monitoring approach multiplies the cost of travel by three compared to adding the same number of sites and using efficient remote monitoring.

10. Don't Enroll More Sites Than You Need

Many studies exceed both timelines and budgets by “overbuilding”—deliberately enrolling what they believe to be an excess of patients. Overbuilding reduces the risk of having an entire study go to waste, but usually burdens a study with unnecessarily long timelines and high costs. The adaptive technique of sample-size re-estimation (SSRE) eliminates both the risk of falling short of the population size required and the risk of wasting time and resources enrolling and treating excess subjects. Sample size can be reduced for a variety of reasons, including observing a larger treatment difference or less variability in data than planners estimated.

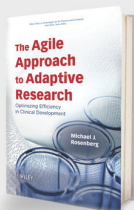
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The adaptive technique of SSRE uses the most efficient methods to enroll just enough patients, and no more. In the breast cancer study described in the contingency planning section, SSRE contributed to time and cost savings by using mid-study data to reduce the study population while also ensuring the ability to demonstrate a difference between the test drug and the comparator.

Health Decisions enrolls 85% of studies on time, compared to the industry average of 10%.

Conclusion

Enrollment will remain challenging in the foreseeable future, and may become even more challenging with the development of greater numbers of personalized medicines. By their nature, personalized medicines target subsets of the population. Recruiting adequate numbers of patients who meet restrictive genetic profiles threatens to increase costs and raise new planning and management issues. However, evidence from the field shows that advanced enrollment practices and tools are up to the challenge of enrolling studies cost effectively and on time.



Additional Resources

Health Decisions' CEO Dr. Michael Rosenberg's book:

[The Agile Approach to Clinical Development: Optimizing Research Efficiency, by Wiley.](#)

Buy now on Amazon

About Health Decisions

Health Decisions is the leading contract research organization (CRO) in Adaptive Clinical Trials committed to shortening development timelines and maximizing pipeline value for pharmaceutical, biotech and medical device companies. Through Agile Clinical Development — a strategic three-pronged approach that combines adaptive design, adaptive operations and proprietary technology — Health Decisions delivers real-time performance metrics that enable sponsors to make the most of competitive market opportunities. Health Decisions is headquartered in Durham, NC, with over twenty years of experience helping sponsors exceed development goals in Phase I-IV clinical trials across all major therapeutic areas.

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