No, Virginia, There Is No Enrollment Problem HS

Bursting the Myth of Late Enrollment

Participant enrollment is the core of effective clinical trial execution. That much is obvious. What is not obvious is why we in clinical research and development have so much trouble enrolling effectively. Numerous publications and conferences devote reams of space and weeks of discussion every year to the topic of "fixing" the enrollment problem. Yet it does not seem to get fixed. The more we try, the more we seem to fail.

But what if there really is no enrollment problem? What if problematic enrollment is just a symptom of a more fundamental problem? What we have discovered is that enrollment is not the problem—it is merely a symptom. This article discusses what we have discovered and how the industry can solve the "enrollment problem" once and for all.

Enrollment is not the problem—it is merely a symptom.

Protocol Execution Involves a Lot of Rework

Figure 1 shows an ideal clinical trial process: We identify potential sites early (once we have a concept sheet), select the best sites for the trial as soon as we have a final protocol, initiate the sites, and then enroll and treat research subjects. But it never seems to work that way. For a seemingly infinite number of reasons, sites are rarely able to enroll as many research subjects as quickly as the sponsors or site administrators expected at the outset.

In fact, the clinical trial usually proceeds as shown in Figure 2. It is the same as Figure 1, with the exception of the yellow and red boxes. When our sites fail to enroll efficiently, we take remedial action by executing some sort of enrollment recovery plan (red box in Figure 2). Whether this recovery plan is executed internally (with sponsor or contract research organization [CRO] staff) or externally (via a specialized recruitment vendor), that red box represents rework—fixing what broke during the enrollment step.

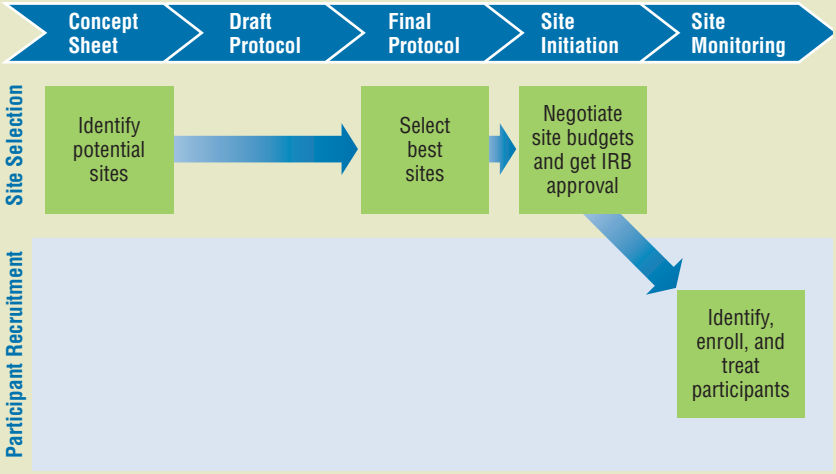
We usually attempt to avoid this problem by surveying sites before we select them, and Figure 2 contains a "site feasibility questionnaire" step (yellow box). This would seem like a reasonable fix for the enrollment recovery task, but in fact it does not work for two reasons:

1. Despite near universal deployment of enrollment feasibility surveys, most trials still have enrollment problems and require enrollment recovery tasks.
2. Virtually no one who uses site feasibility surveys believes in the results. Clinical trial managers either divide the survey number by three or four, or

HS Home Study article

Beth Harper and Dave Zuckerman disclose that they have no actual or potential conflict of interest in relation to this article.

Figure 1 The Way Clinical Trial Execution Should Work



even by 10, or they ignore the results in favor of their own enrollment forecast.

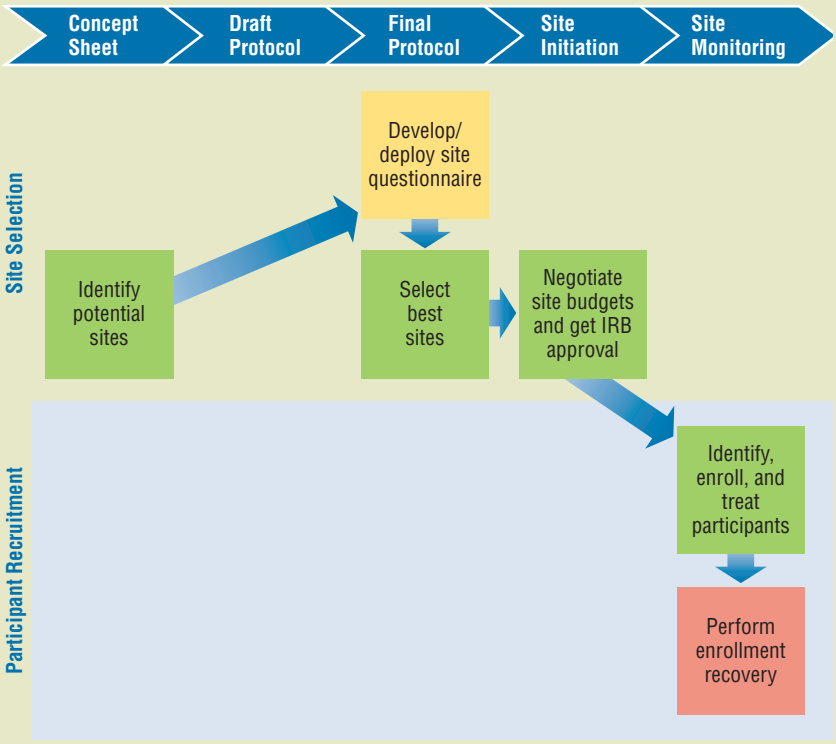
From a process perspective, this situation is a classic result of trying to fix the symptom rather than the fundamental problem.

The Fundamental Problems

There are actually not one, but two fundamental problems, and neither is participant enrollment:

1. The protocol is rarely designed with participant enrollment and protocol execution in mind, so it is difficult for even the most efficient and effective sites to enroll.
2. The execution team does not have a clear, unambiguous vision of what constitutes an ideal site for a given trial and how best to support that site in its enrollment efforts.

Figure 2 The Way Clinical Trial Execution Actually Works



Here is some evidence that these two are indeed the fundamental problems:

- One of the first things that clinical teams do when enrollment lags is to look at the protocol and identify what aspects can be modified to make enrollment easier. Inclusion/exclusion criteria are the first target, but sometimes visit schedules and procedure lists are also causing problems.
- The team visits sites to accumulate data on what is working and what is not. It then publishes newsletters, hosts teleconferences, and commences booster visits to spread best practices.
- The team goes on a booster visit binge or runs a rejuvenation meeting in an attempt to encourage sites and enhance enrollment.
- The team initiates additional sites that it hopes have the characteristics of the high-enrolling sites and lack the characteristics of the low-enrolling sites.

Indeed, all of the steps that clinical teams take to fix low enrollment point directly to these same two fundamental problems. Thus, if we can "optimize" the protocol for enrollment and then "customize" the site selection and support process for the protocol at hand, the enrollment problem will, in fact, vanish.

This view of the problem flies in the face of current thinking about enrollment, and might seem nonsensical. An analogy that will help to clarify this new perspective is consumer credit card debt. Consumers who are in debt are typically offered ways to reduce the debt and associated monthly payments (e.g., roll the debt into a lower interest loan). However, debt is not the

If we can "optimize" the protocol for enrollment and then "customize" the site selection and support process for the protocol at hand, the enrollment problem will, in fact, vanish.

problem; it is only the symptom. The real problem is out-of-control spending, which leads to that debt. If we fix the spending problem, the debt problem will not recur. But we can go even one step further: If we avoid spending problems in the first place (by planning a realistic budget and prioritizing our needs and wants), the debt problem will never occur at all.

Enrollment is the "debt"; protocol and site selection problems are the "out-of-control spending"; and there are specific steps to avoid the enrollment problem in the same way as there are steps to avoid the debt problem. With each new protocol, we have the option to avoid the enrollment problem by optimizing the protocol to maximize enrollment and selecting only those sites that have a high probability of enrolling, given the specific requirements of that protocol.

A Better, More Efficient Approach

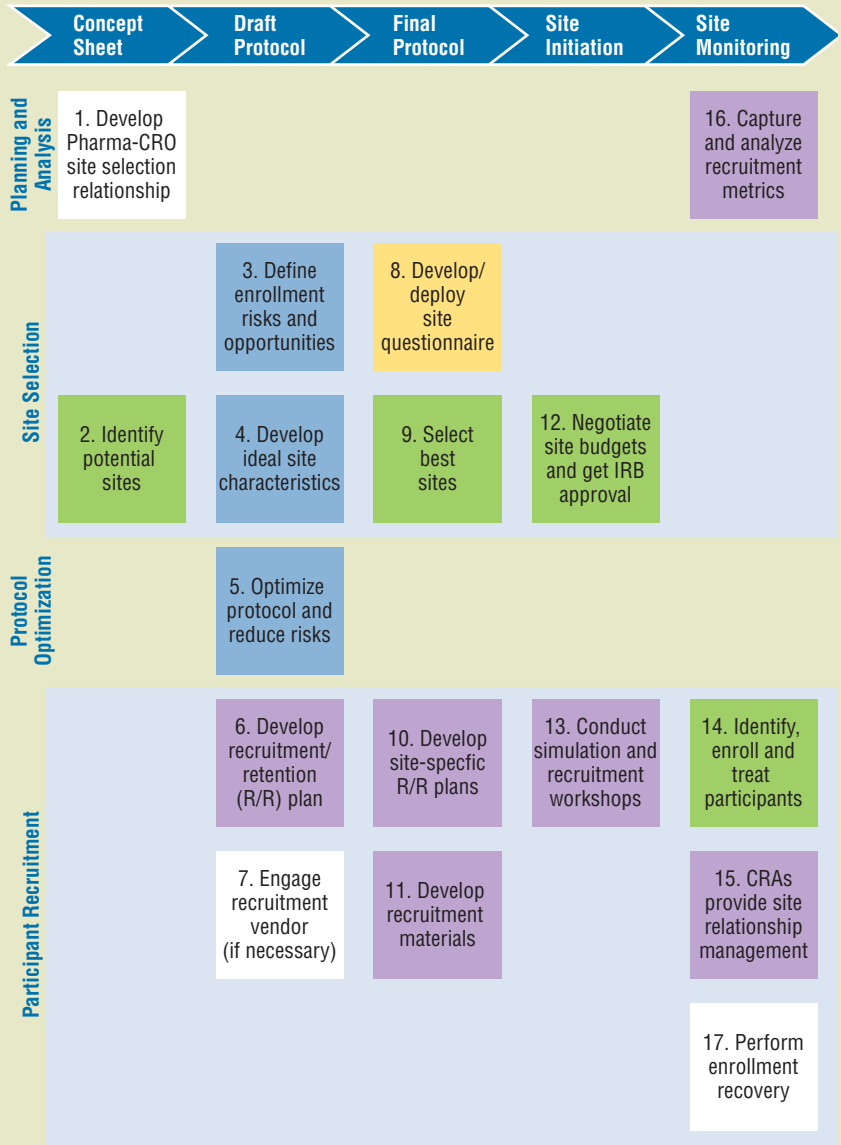
How can this actually be accomplished? Figure 3 shows the overall process. Although this new process looks daunting, most organizations already perform at least some of the steps and may only need to perform them more effectively. Just as debt avoidance requires a systematic, disciplined approach to spending, this combination of steps, in this order, and with a sufficient level of disciplined execution will ensure successful enrollment.

First, note the different colors of the boxes:

- The green and yellow boxes are the ones shown in Figure 2.
- The three blue boxes are geared toward identifying characteristics of sites appropriate to the protocol and characteristics of the protocol that make it difficult to enroll.
- The six purple boxes are geared toward ensuring that the clinical team has the best possible approach for supporting sites in enrollment and ensuring that sites are doing an effective job.
- The white boxes represent optional tasks that the team may also need to undertake if engaging a CRO or patient recruitment service provider in the study execution process. Note that box 17, which was red in Figure 2, is now white, because it is no longer a rework step but an option for improving enrollment.

Here is a closer look at all 17 steps:

Figure 3 Accomplishing On-time Enrollment without Need for Recovery



1. **Develop a sponsor–CRO site selection relationship:** Both the sponsor and the CRO must—early in the process—have a mutual understanding of who will handle what part of enrollment and who has responsibility and authority for making what decisions. When a CRO helps vet the protocol, that CRO is likely to do a much better job of execution, since it has lent its expertise to avoid execution problems.
2. **Identify potential sites:** As soon as you have a protocol draft or concept sheet, you need as complete a list of potential sites as possible (including all potential countries). Do not be concerned about selecting the "best" sites yet. Some sponsors wait until site initiation to create their site list (too late); others try to shorten the list before the protocol is finalized (too early). The goal here is to develop as large a list as possible so that you can begin to determine which of the potential sites will be most effective.

   For example, a pharmaceutical company focused on tertiary care sites for a particular protocol. Late in protocol development, a need for drug-naïve subjects surfaced and the pharmaceutical company then had to go back and start looking for primary care sites (which turned out to be very difficult to find). If the company had developed a full site list at this early stage, the drug-naïve requirement would have taken much less time to address.
3. **Define enrollment risks and opportunities:** Once you have a draft protocol, you can determine what is going to drive site enrollment and what is just going to drive the sites crazy. This is a critical step that can make a significant difference in enrollment. It is *not* a feasibility survey; instead, it is a carefully structured, methodical, in-depth interview with less than a dozen sites, the goal of which is to figure out what will make a site successful for this specific study. A given site or site type might enroll very well for one study and poorly for the next. Standards of care may change, care pathways may vary, subject volumes may increase, or specific procedures or visit schedules may require a different site type. Only by a careful evaluation of the type of site appropriate for a given study can a sponsor identify the enrollment risks and opportunities.

Once you have a draft protocol, you can determine what is going to drive site enrollment and what is just going to drive the sites crazy.

4. **Develop ideal site characteristics:** Once you have defined the risks and opportunities in enrollment, you can determine the characteristics of an ideal site and, importantly, the characteristics of a low-enrolling site. This analysis can save literally millions of dollars and many months of enrollment by avoiding most low-enrolling sites. The risks and opportunities analysis of Step 3 will provide many clues as to how different site types will perform.

   Do the sites think that indigent or wealthy subjects are most likely to enroll? Will the subjects tend to be younger or older? Will they come from the community at large or from captive patient populations? Will the screening procedures require multiple visits or can they be done in a single visit? These and multiple other questions can be answered by the sites and will indicate whether the best site is inner city, suburban, or rural; academic, hospital-based, or standalone private practice; have an older or younger patient panel; be in the U.S. Northeast or Southwest, etc. The actions suggested by the data are often counterintuitive, but will lead to elimination of most non- or low-enrolling sites and to the initiation of more high-enrollers.
5. **Optimize protocol and reduce risks:** Knowing what drives site performance for this protocol, we can adjust the protocol ("optimize" it) to maximize the potential for enrollment. Seemingly minor aspects of a protocol can wreak havoc on enrollment; this step allows you to systematically avoid them. For instance, a sponsor thought that a protocol that used a new, in-office lab test would make the site's work easier, but the sites realized that its high false-positive rate would disqualify otherwise viable enrollees. Feedback from the sites caused the sponsor to remove the new test from the protocol and reinstate the traditional central lab approach.
6. **Develop a recruitment/retention plan:** To determine the best recruitment and retention plan, the team should address all of the important factors in clinical trials participation: building study awareness, educating the research subjects and their families and potential influencers about the trial, and ensuring that all site staff are credible and responsive to all research subject needs. The goal is to do everything possible to reduce study risks and minimize the burden of participation.
7. **Engage a recruitment vendor:** By this point, you will know if enrollment for this protocol is going to be a walk in the park or a climb up a sheer cliff. If it looks like it will be a vertical climb, Steps 3 through 6 will provide enough information so that you can effectively engage a recruitment vendor—before enrollment goes off track.

8. **Deploy site questionnaires and conduct feasibility assessment discussions:** Now you can proceed with more traditional study feasibility assessments. Using a combination of questionnaires and conversations is advisable, and study feasibility assessment must be evaluated over the course of protocol development, rather than at a single point in time (see Table 1). The questions will not be standard, but will be derived from the research in Steps 3 through 6, and are geared toward finding those sites that most closely match the ideal site characteristics (see Step 4).
9. **Select the best sites:** This step is now almost perfunctory, because you know exactly what you are seeking. However, you now have a significant advantage: You can select fewer sites than most sponsors currently require, because you can select only the best, and you have greater confidence that they will enroll.
10. **Develop site-specific recruitment and retention plans:** Once the general recruitment and retention plan is in place, customize the plan for each site to meet its needs. Be sure to document the plan in writing. If it is not documented, it will not get done.
11. **Develop recruitment materials:** Based on the needs of the study, recruitment and retention support materials must be developed. This requires a balance of art and science to identify appropriate creative concepts, messaging, and study brands while creating materials that have a professional look and feel.
12. **Negotiate site budgets and acquire institutional review board/ethics committee approval:** Everything should proceed more smoothly now that the sites are well aligned with the protocol requirements.
13. **Conduct simulation and recruitment workshops:** In addition to the robust enrollment optimization and planning efforts, the likelihood of success can be increased if both site staff and clinical research associates (CRAs) are trained in effective implementation strategies and techniques. It is critical to move beyond the traditional investigator meeting where sponsors typically share information via PowerPoint presentations. Instead, employing interactive workshops enables sites and CRAs to work together to practice or simulate complex protocol procedures in a safe environment.
14. **Identify, enroll, and treat research subjects:** The sites now have the necessary tools, skills, and budget to implement their recruitment and retention plans and get down to the business of enrolling and managing research subjects.
15. **CRAs provide site relationship management:** Maintaining a positive and productive site relationship is as important as having a well-structured recruitment plan. This requires finesse in terms of building intentional relationships with the sites, along with a strategic site communications plan to keep the study at the forefront of each site's mind.
16. **Capture and analyze recruitment metrics:** Once a plan is developed, it should be considered a "roadmap" to success that can be adjusted as the enrollment process unfolds. Fluidity and flexibility are

Table 1 Study Feasibility Assessment Continuum

Study Feasibility Questions to Address During:

Concept Stage	Draft Protocol Stage	Final Protocol Stage
Best and worst case enrollment scenarios?	Site comfort level about approaching patients and family about the study opportunity?	Expected ethics approval timelines?
Potential barriers to enrollment and retention?	Site perception of budget adequacy?	
Access to the appropriate patient population?	Planned recruitment and retention approaches?	
Site experience?	Perceived site training needs?	
Site interest?	Adequacy of site staff and resources?	
Site comfort with the research design?	Site perception of administrative burdens associated with conducting the study?	
Site perception of risk to subjects?	Access to appropriate equipment and facilities?	
Likelihood of ethics approval and potential "non-negotiable" factors?		
Opportunities to make the protocol more operationally efficient?		

key when it comes to the actual implementation of the plan. Recruitment performance should be tracked at the initiative (or tactic), site, region, and study levels to identify trends, best practices, and opportunities for improvement.

17. **Perform enrollment recovery:** If you follow steps 1 through 16, you will not need to worry about enrollment recovery, terminating relationships with sites, finding new sites, etc. Proceeding correctly from the very beginning is all about preventing problems down the road.

The Bottom Line

Using this methodology costs only a few weeks up front, and can save months or years and millions of dollars down the road. In fact, costs can be far less than that of a single amendment or a couple of low-enrolling sites. However, this process does require planning and discipline, and every team should carve out the time to do it right. The enhanced enrollment will more than reward the effort. A single amendment typically costs $200,000, and each site that is initiated, monitored, and closed out costs $50,000. On the other hand, the process described here costs $50,000 to $150,000 to perform. Thus, one less amendment (due to a cleaner protocol) or two or three fewer non-enrolling sites (due to better site selection and support) pays for the cost of all of these steps. Several sponsors have begun using these techniques and have found their returns on investment for this work to be more than 3,000%.

Several sponsors have begun using these techniques and have found their returns on investment for this work to be more than 3,000%.

We welcome your thoughts on this critical subject. Once you have tried the techniques we outline, let us hear about your successes or failures in using them. With time, experimentation, and honest discussion, we are convinced that the "enrollment problem" can be overcome once and for all. Please e-mail us with your experiences and breakthroughs. **ACRP**

Beth Harper is president of Clinical Performance Partners, a clinical research consulting firm specializing in enrollment and site performance management and facilitating productive sponsor-site relationships. She is also an adjunct assistant professor in the Clinical Research Administration Program of the School of Medicine and Health Sciences at George Washington University, and can be reached at bharper@clinicalperformancepartners.com.

Dave Zuckerman is president of Customized Improvement Strategies LLC, a consulting firm that supports clients in process streamlining, teambuilding, and organizational change. He lectures internationally on research and development metrics, Balanced Scorecards, and protocol development, and has published a number of magazine articles on metrics, protocol development, and research and development risk reduction. He is the author of *Pharmaceutical Metrics,* published by Gower Press in 2006, and can be reached at dave@rx-business.com.